SURGERY

VOL. 45 APRIL, 1959 No. 4

Original Communications

THE REVERSE PORTACAVAL SHUNT

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IN A recent study of hepatic metabolism in dogs,[8] an experimental preparation was established in which the entire deep femoral venous return passed through the liver. This was accomplished by the formation of a side-to-side portacaval fistula, ligation of the inferior vena cava proximal to the anastomosis, and removal of the caval and iliac collaterals. Because of the potential value of this procedure in other studies of liver function, the method will be described.

METHOD

Five mongrel dogs, approximately 10 Kg. in weight, were selected. Under sodium pentobarbital anesthesia the abdomen was entered through a long upper midline incision. The stomach and intestines were displaced down and to the left. Adequate exposure of the operative site was obtained by upward retraction of the liver after the thin mesenteric veil of the caudate lobe was sectioned. (Fig. 1.) The portal vein and the vena cava were prepared for anastomosis and a preliminary untied ligature was placed around the proximal cava. The small bile duct tributary that crosses the portal vein was avoided. The anastomotic site was selected well above the renal veins and two guide sutures placed at least 1 cm. apart through the wall of both the portal vein and the inferior vena cava. The sutures were tied to approximate the vessels and a modified Potts clamp[6] was positioned to provide partial occlusion of both veins. An elipse was excised from the wall of both

Received for publication Aug. 25, 1958.

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vessels and the anastomosis was carried out with continuous 5-0 arterial silk (Fig. 1). The partial occlusion clamp was removed and the vena cava was then tied and transected well above the entrance of the adrenal veins. When the anastomosis was adequate, there was no distention of the distal vena cava.

Two to three weeks after surgery, dye studies were done by injecting 90 per cent Hypaque sodium into the femoral vein. Only a portion of the injected material reached the hepatic bed. The remainder bypassed the liver via extensive collaterals which originated from inferior vena cava branches (Fig. 2). A second procedure was then done on three of the five dogs and all venous tributaries from the site of caval ligation through the hypogastric veins were divided with the exception of the renals. Dye studies two to three weeks after reoperation revealed that all material injected into the femoral vein passed directly through the anastomosis into the liver (Fig. 3). Inferior caval pressures in two dogs, obtained three weeks after the second procedure, were 140 and 160 mm. saline, respectively.

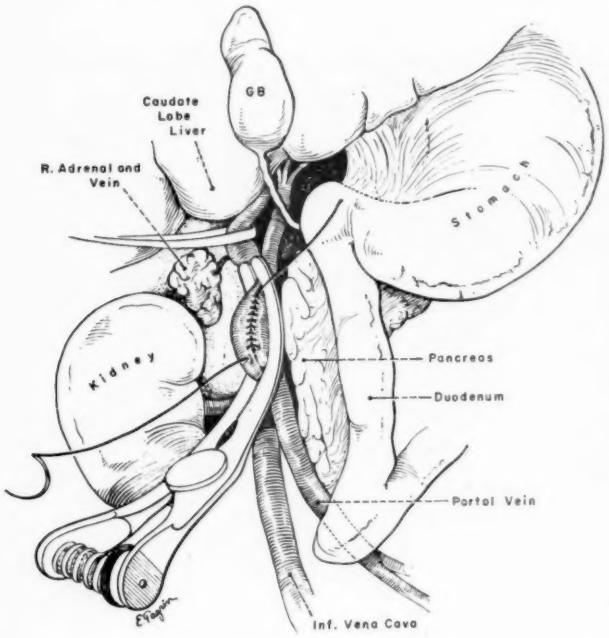

Fig. 1.—Artist's view of side-to-side portacaval anastomosis in formation of reverse Eck fistula.

DISCUSSION

These procedures were not detrimental to the health of any of the five dogs. Oliguria, edema of the hindquarters, or ascites did not develop. Except for an increase in prominence of the superficial veins of the abdominal wall, the dogs were indistinguishable from normal animals. Previous investigators have described the absence of harmful sequelae after reverse Eck fistula.[1, 3, 4, 5, 7] It is evident, however, from the present venographic studies that the usual reverse Eck fistula provides incomplete diversion of caval blood

flow into the portal system due to the rapid development of systemic venous collaterals. Division of these collaterals was not attended by an increased morbidity in the present series.

Since diversion of large quantities of systemic blood through the portal system is not injurious to liver function,[2, 9] impaired hepatic metabolism in the present circumstances would be surprising. The absence of any morbidity or mortality is of interest, however, inasmuch as the adrenal venous drainage

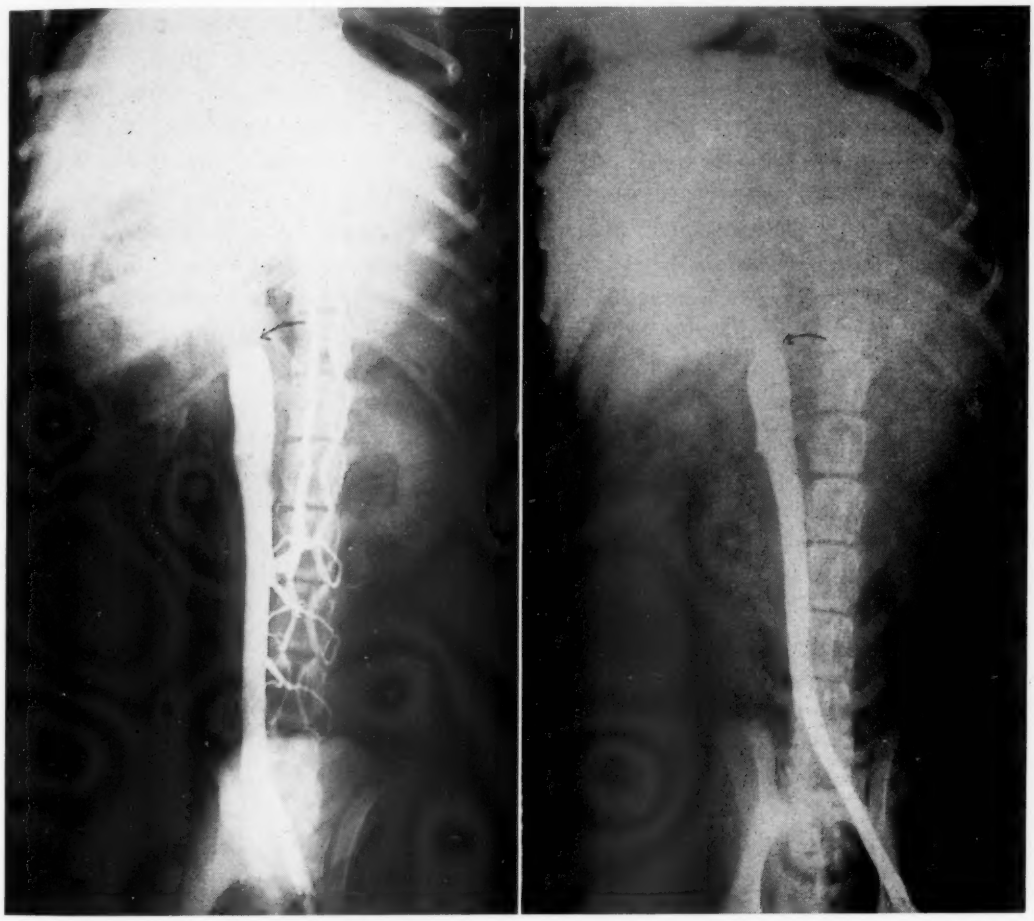

Fig. 2. Fig. 3.

Fig. 2.—Distribution of 90 per cent Hypaque during injection into the femoral vein in a dog with reverse Eck fistula. Note the development of large systemic venous collaterals with resultant incomplete diversion of caval flow into the portal vein. The anastomosis is marked with an arrow.

Fig. 3.—Hypaque injection into the femoral vein (same dog as Fig. 2) three weeks after caval-iliac strip. Note that the entire dose of dye passes through the anastomosis (arrow) into the liver.

was shunted through the portal bed. In commenting on the difficulty of obtaining survivors in portacaval transposition, Summers, Malette, and Eisman[10] have implicated the passage of endogenous adrenal hormones through the hepatic parenchyma as the principal cause of death. The present findings do not support this concept.

The described technique of altering the venous drainage of the inferior half of the body has application in the experimental study of certain phases of hepatic metabolism. Ordinarily, when repeated intraportal injections of any substance are desired, it is necessary to perform multiple celiotomies or splenic punctures. With the present preparation, injections can be made into the leg veins of the unanesthetized animal and all the material will pass through the reverse Eck fistula into the liver bed. For such studies to be valid it is necessary to interrupt the entire caval collateral (Figs. 2 and 3). If desired, the effect of systemic venous administration can then be compared in the same dog by injection of the substance into a forelimb vein. The role of the liver in the physiology of hormones or other drugs can thus be conveniently studied. This method also affords a means by which hepatoxic drugs can be repeatedly instilled directly into the portal circulation in an effort to produce experimental cirrhosis.

It is interesting to speculate about the occasional clinical situation to which the principal of caval-portal rerouting may be applicable. The most obvious possibilities would be neoplastic invasion of the inferior vena cava between the renal veins and the diaphragm, or traumatic injury in this area severe enough to necessitate sacrifice of a segment of the vessel. It would be tempting, under these circumstances, to anastomose the distal end of the cava to the side of the portal vein rather than accept the high risk of failure of interposing a replacement vein graft.

SUMMARY

A technique has been described in which all the venous drainage of the deep femoral system is diverted through the hepatic bed by means of a reverse Eck fistula and systematic division of collaterals from the inferior vena cava and iliac veins. The use of this technique in the study of liver metabolism is proposed. Employment of simple reverse Eck fistula is suggested in clinical situations in which there is subdiaphragmatic destruction of the inferior vena cava.

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COMMON BILE DUCT ANASTOMOSIS

An Experimental Study

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SURGERY of the common bile duct continues to present numerous problems. Stricture formation and leakage of bile following an anastomosis are among complications as yet unsolved.[1, 3, 14] The suggestion that an end-to-end everting anastomosis might be less prone to stricture formation[2, 12] and the renewed interest in primary closure of the common duct without postoperative T-tube drainage[5, 9] prompted this study of various types of common duct anastomoses under conditions of stress.

MATERIALS AND METHODS

Thirty healthy mongrel dogs weighing between 8 and 10 Kg. were subjected to a series of two operations.

At a preliminary operation, under intravenous Nembutal anesthesia (30 mg. per kilogram) and through a right paramedian incision, the porta hepatis was exposed and the common bile duct obstructed. With 3-0 silk sutures the common bile duct was doubly ligated in continuity just proximal to its entrance into the duodenum (Fig. 1). The dogs were allowed to eat and drink after recovery from anesthesia. No special postoperative measures were instituted. All dogs survived this procedure without undue morbidity. With the exception of two dogs, they did not develop clinical jaundice, although their serum bilirubin and icteric index rose compared to the preoperative control values.

One week after common duct obstruction, and without any special preoperative preparation, each of the 30 dogs was subjected to a second operation which consisted of transection and anastomosis of the common bile duct. Under intravenous Nembutal anesthesia and with artificial respiration being maintained through endotracheal intubation, a right transthoracic approach was utilized, since in the dog the transthoracic approach provides excellent exposure of the extrahepatic biliary tract without undue morbidity or prolongation of the procedure. The chest was entered through the ninth interspace, and the right leaf of the diaphragm incised, bringing the lobes of the liver, the common duct and biliary radicles, pancreas, and duodenum directly into view.

Aided by Research Grant #E-524(C4) from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health, Public Health Service, and by a grant from the Edward G. Schlieder Educational Foundation.

Received for publication Aug. 25, 1958.

The gall bladder, hepatic, and common bile ducts were markedly tense and dilated. The common duct measured between 10 and 15 mm. in diameter, compared to the normal diameter of 2 to 3 mm. The distended common duct was decompressed by needle aspiration of 40 to 70 c.c. of bile (Fig. 2).

The common duct was cleanly divided about 2 cm. proximal to the previous site of occlusion, which was not disturbed. Three different forms of anastomoses were performed in three groups of 10 dogs each (Fig. 3). In all anastomoses 5-0 silk was utilized.

In Group A, the common duct was anastomosed with a single, continuous, inverting suture interrupted at two points.

In Group B, a continuous, over-and-over suture was used.

In Group C, a continuous, everting anastomosis was performed.

No tubes were placed in the common duct for support and no drains were left either in the chest or the peritoneal cavity.

The diaphragm was repaired and the chest incision closed anatomically.

All dogs recovered from anesthesia and no special supportive measures or antibiotics were used in the postoperative period. Surviving animals were sacrificed from two weeks to two months after the second operation. Careful postmortem examinations were conducted on these as well as on those animals which died prior to the time selected for sacrifice. At the time of sacrifice cholangiograms were obtained by introducing 30 per cent Diodrast through a polyethylene tube inserted into the common duct.

Serum bilirubin and icteric index were determined on all dogs just before the first and the second operations and before sacrifice of those animals which survived.

RESULTS

All 30 dogs survived the first operation in which the distal common bile duct was ligated in continuity.

Of the 10 dogs in Group A, in which the inverting technique was utilized for the common bile duct, 8 survived and 2 died. One died with generalized peritonitis due to a 2 mm. perforation at the anastomosis, and one with a large duodenal ulcer and malnutrition on the fifteenth and fourteenth postoperative days, respectively.

Of the 10 dogs in Group B, in which the common bile duct was anastomosed by the over-and-over technique, 8 survived. Two died on the tenth postoperative day: one with generalized peritonitis due to a leak at the anastomosis (this dog also had postoperative hemothorax), and the other because of empyema, pneumonitis, and a small leak at the anastomotic site.

Of the 10 dogs in Group C, in which an everting technique was used for anastomosis of the common duct, 4 survived. Six died from 6 to 14 days after surgery because of generalized bile peritonitis due to disruption at the anastomotic site. When the common bile ducts of these animals were examined at postmortem, only a thin layer of mucosa bridged the anastomosis.

The three different types of anastomoses produced no appreciable difference in the size of the lumen of the duct.

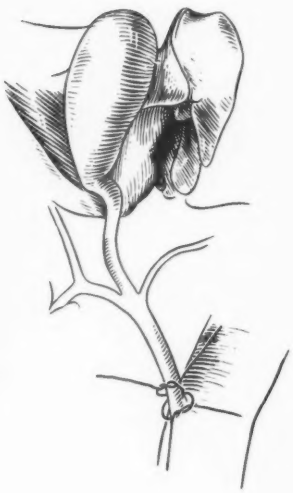

Fig. 1.

Fig. 2.

Fig. 1.—Diagram of ligation of distal common bile duct in continuity.

Fig. 2.—Aspiration of distended common bile duct at second operation, one week after obstruction.

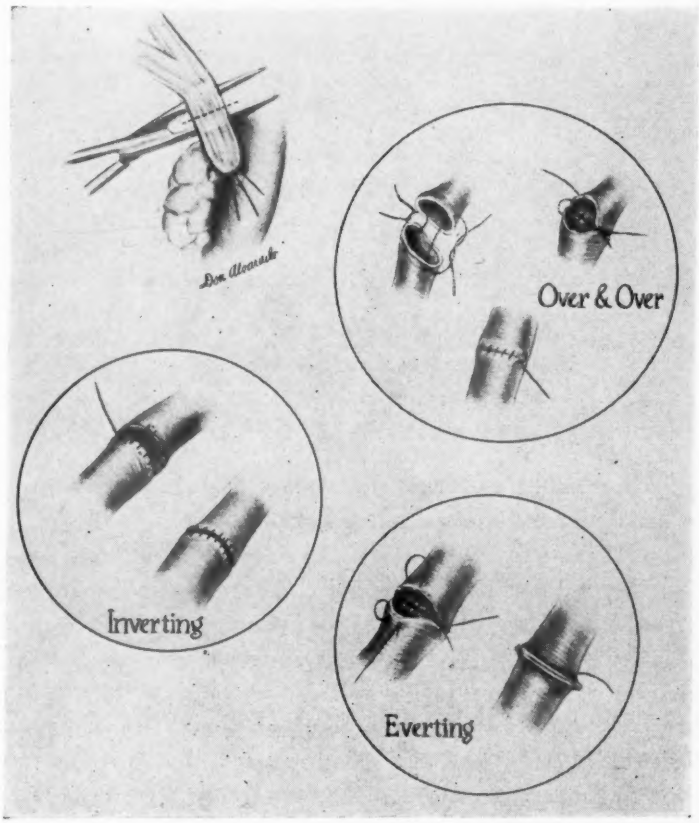

Fig. 3.—Top left: division of the obstructed common bile duct proximal to the ligature. The inserts reveal the three types of anastomoses used in this study.

At sacrifice, the animals from the three series showed almost identical gross and microscopic findings at the site of the common duct anastomosis, and one could not tell them apart (Fig. 4). There was minimal scarring and constriction at the suture line. The mucosa of the duct appeared smooth and intact (Figs. 5 and 6). The ligated common duct had recanalized in those animals which survived, as judged by the fall in serum bilirubin, icteric index, cholangiogram, and findings at sacrifice (Fig. 7). In those that died, the patency of the common duct could not be determined because of considerable surrounding inflammatory reaction.

The distal site of obstruction revealed marked scarring in which was embedded the occluding ligature that had cut through. However, the duct could be dissected out and its patency determined by a probe.

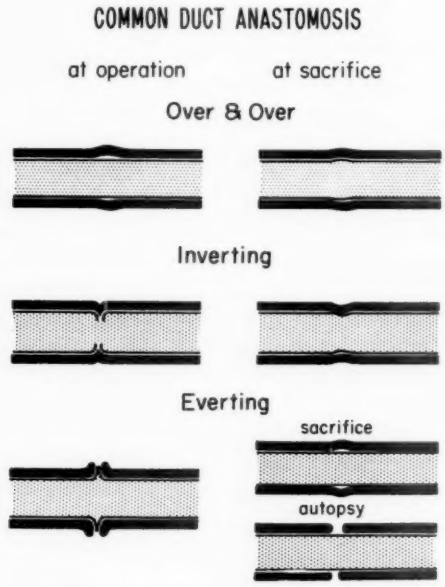

Fig. 4.—Diagrammatic representation of the three types of anastomoses at operation and at sacrifice. Note that there is little difference in the contour of the anastomoses or the size of the lumen at sacrifice. The everting type anastomosis when followed by death is shown in the lower diagram. Autopsy reveals failure of healing of the seromuscularis although the anastomosis is partially bridged by mucosa.

In spite of its recanalization and the lack of biliary precipitate, the common duct remained dilated for as long as two months without producing any overt symptoms in the survivors in each group. With time the duct size decreased toward normal. Since none of the animals were observed over two months, the total time for the ducts to return to normal could not be determined. This increased intrabiliary pressure was not associated with any gross changes in the liver.

The continuous type of suture, interrupted at two points, used in these experiments for expediency, did not produce any demonstrable "purse-string" effect. In fact, the anastomotic site took part in gradual dilatation of the common bile duct due to distal obstruction. In some of the autopsy specimens, the sutures were "bowed" inside the lumen of the ducts (Fig. 8).

DISCUSSION

We undertook this experimental study for two reasons. The first was to determine if suture technique makes any difference in the short- and long-term healing of a common bile duct anastomosis in the presence of distal obstruction. The second reason was to determine if a T tube is necessary for safe healing of the anastomosis under the unfavorable condition of increased pressure from biliary obstruction.

Fig. 5.

Fig. 6.

Fig. 5.—Extrahepatic biliary tree of one of the dogs at sacrifice. Site of obstruction of the distal common duct is shown by the arrow. Common bile duct anastomosis pointed out by the hemostat. Note marked dilatation of the common duct and lack of constriction at the anastomotic line.

Fig. 6.—Marked dilatation of the common bile duct proximal to the ligated site. The lack of stricture at the anastomotic site is shown by the arrow. (See text for description.)

A search of the literature failed to disclose a detailed description of the mucosal approximation technique commonly recommended for common bile duct anastomosis, a procedure which may not be uniformly understood and practiced in similar fashion by various surgeons. A complete mucosal approximation technique is an everting mattress suture, either interrupted or continuous (similar to that used by the vascular surgeons for the intima-to-intima approximation).[2] This form of suture technique in our experience

proved to be associated with poor healing, frequent disruption of the anastomosis, and a 60 per cent mortality. A simple over-and-over technique which is neither a complete mucosal nor a complete serosal approximation technique, and the inverting suture which primarily approximates the seromuscularis, gave the best results, with 20 per cent mortality. No stricture or stenosis was produced with these suture techniques and only three leaks occurred in 20 dogs.

Since the experimental work of Sullivan[13] and his use of tube splints and the popularization of the T tube by Mayo,[10] Lahey,[6] and others, these adjuncts to common bile duct surgery have been widely accepted and used.

Fig. 7.

Fig. 8.

Fig. 7.—Cholangiogram of a dog at sacrifice 42 days after common bile duct obstruction followed by a proximal division and reanastomosis of the duct. The white arrow points to the site of distal obstruction. Note that the duct had recanalized and the radiopaque substance has entered the duodenum. The black arrow points to the site of division and anastomosis. Note minimal narrowing at this site.

Fig. 8.—A typical obstructed common bile duct at sacrifice. The polyethylene tube is threaded through the intramural portion of duct beyond the doubly ligated site into the greatly dilated proximal common duct. Note that the continuous suture of the anastomosis has "bowed" in the lumen of the duct.

However, discontent with the use of foreign body splints during the healing of anastomoses has been voiced from time to time. Every surgeon can cite examples of complications related to the use of these materials. The major disadvantages of the T tubes commonly listed are: (a) stricture formation, (b) bile precipitation and occlusion of the tube, (c) leakage of bile around the tube or because of its premature removal, (d) ascending infection, and (e) pancreatitis when long tubes are used.

The experimental work of Harridge[4] indicates that stricture formation is not due to irritation of the common duct wall by the foreign body splint, but rather due to the decompression effected by the T tube. Bile under pressure apparently exerts a gentle dilatory effect. No stricture was found in those experimental subjects in which the long limb of the T tube was clamped off.

The occlusion of T tubes by the precipitation of the bile products has been a rather common experience when the tubes are left for long periods. According to Lahey,[7] the nature of the material of which the tube is made is not a major factor. Bile precipitation occurs in rubber tubes as well as in plastic and Vitallium tubes.

The use of the T tube does not obviate leakage of bile and peritonitis. Clinical records as well as experimental work contain such instances.

Bile peritonitis in these studies (with inverting or over-and-over sutures) was no more common than in other experimental work which utilized the T tube.[8, 11] This observation is significant especially in the light of the fact that in our study the anastomosis was performed in the presence of distal obstruction of the common duct and that no external drainage was provided, while in other studies obstruction was released before the anastomosis was performed and the peritoneal cavity was drained.

One might argue that bile leakage around the T tube or because of its premature removal is due to technical errors which might be avoided if more care were exercised. On the other hand, errors from these sources would not exist if T tubes were not used.

The problem of ascending infection through the tube is a theoretical hazard. Although no controlled clinical studies have been undertaken, no grave complication from this source has been reported.

Acute pancreatitis, secondary to the use of long T tubes, is a rare complication, and its discussion probably is not pertinent here.

We readily admit that these severe experimental conditions are not directly applicable to clinical surgery. One does not knowingly perform an anastomosis in the presence of distal obstruction. However, a stone may be overlooked or edema of the sphincter of Oddi may be produced following instrumentation. In either case, partial obstruction of bile flow may exert pressure on the anastomosis and produce a problem comparable to these experimental conditions.

To approach a clinical situation we could have resected the obstructed site, but the discrepancy in the size of the lumen would have made an end-to-end reanastomosis impossible.

While transfer of these results to the human patient is voiced with caution, these findings in conjunction with other recent reports may justify further clinical trial of elimination of T tubes and splints in certain selected categories of biliary surgery.

SUMMARY AND CONCLUSION

A plan was devised to study various types of common duct anastomoses under conditions of stress.

At a preliminary operation in 30 dogs, the common duct was ligated next to the duodenum and the dogs were arbitrarily divided into three groups of equal size.

One week later the common duct was divided and reanastomosed by either an inverting, an over-and-over, or a true everting technique. The obstructing ligature was left in place. No form of drainage was employed and no antibiotics were used.

In each group of the inverting and the over-and-over type of anastomoses the mortality was 20 per cent. No stricture or stenosis was produced at the site of anastomosis with these suture techniques and only three leaks occurred in 20 dogs.

In contrast, the mortality was 60 per cent in 10 animals with a true everting anastomosis. These animals succumbed to a complete disruption of the common bile duct anastomosis and subsequent bile peritonitis.

It is concluded that, in the experimental animal with a distal common duct obstruction, (a) both the inverting and the over-and-over suture techniques are satisfactory for common duct anastomoses and neither will result in stricture or stenosis, (b) the everting type of anastomosis of the common bile duct is not safe and will result in poor healing and frequent disruption of the anastomosis, (c) the T tube is not essential for the safe healing of common bile duct anastomoses, and (d) the use of a continuous nonabsorbable suture is undesirable for common duct anastomoses.

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A COMPARATIVE STUDY OF VARIOUS MECHANISMS OF HEPATIC RESTORATION IN THE RAT

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THE ability of the liver to restore itself after partial removal has long been of interest to biologists and physiologists. In rats, dogs, and other animals, removal of up to 70 per cent of the liver is followed by growth of the remaining lobes re-establishing normal liver volume and the new parenchyma is by all criteria normal hepatic tissue.[4, 6] Pathophysiologic studies of experimental cirrhosis have revealed a similar process after focal injury or destruction.[9] With the advent of extensive hepatic resection by Brunschwig,[2] Pack,[10] and others, it has become apparent that the human liver also restores itself after major resection by an increase in size of remaining liver.

The mechanism by which this new, apparently normal, hepatic tissue is produced has been studied extensively by Stephenson,[13] Mann,[5, 7] and Grindlay and Bollman.[3] Most reports favor an increase in portal flow through the remaining lobes as the causative mechanism for this impressive restoration. Failure of restoration after partial hepatectomy in the presence of an Eck fistula[5, 7, 8] is important supporting evidence for this concept. It has been shown also that ligation of the portal venous supply to a portion of the rabbit liver results in marked local atrophy with corresponding hypertrophy of the remaining liver.[11, 12]

It has been suggested that the intense restorative or regenerative response that occurs following partial resection of the liver might be utilized with benefit in patients afflicted with cirrhosis. Although there are obvious objections to such an extensive surgical procedure in patients with advanced cirrhosis, the concept of encouraging growth of new liver by surgical procedures is intriguing. If the growth of new liver is entirely due to changes in portal flow, occlusion of a major tributary of the portal inflow to the liver should produce the same result as removal of the liver supplied by this portal branch. Both procedures, however, would probably have a deleterious effect on portal pressure and this is often the major problem with cirrhosis that the surgeon is called upon to manage. Bax[1] has reported early trials of initiating hepatic regeneration in patients by ligation of the hepatic duct to a portion of the liver. Although he has no definite evidence of clinical benefit as yet, he is applying this operation to selected cases of cirrhosis on the basis of findings in both normal and cirrhotic rabbits.[12]

This work was supported by a grant from the U. S. Public Health Service, N.C.I.-9261.
Received for publication Sept. 15, 1958.

Since the experimental evidence available at present seems insufficient to form conclusions regarding the possible value of any surgical procedure to induce liver restoration, any clinical application would require previous clarification of several aspects of this process: (1) Are there factors other than changes in portal pressure or flow that contribute to restoration after partial resection of the liver, and (2) how does the regenerative or restorative response following partial hepatectomy compare in a quantitative sense with that induced by ligating portal venous supply or the hepatic duct to the same volume of liver?

METHODS

This study was comprised of approximately 230 female white Wistar rats that survived the surgical procedures to be described. The initial body weights were 125 to 175 grams. They were fed a standard well-balanced commercial diet* throughout the period of study. All operations were carried out under ether anesthesia using aseptic technique. The procedures performed are listed in Table I.

TABLE I

GROUP	NUMBER OF RATS	PROCEDURE PERFORMED
A (Control)	70	Midline abdominal incision
B	40	Excision left and median lobes, ligating the pedicles with silk; this excised tissue represented 65 to 70 per cent of liver mass
C	48	Ligation of hepatic duct draining left and median lobes
D	45	Ligation portal blood supply to left and median lobes
E	25	Ligation portal and arterial blood supply to left and median lobes

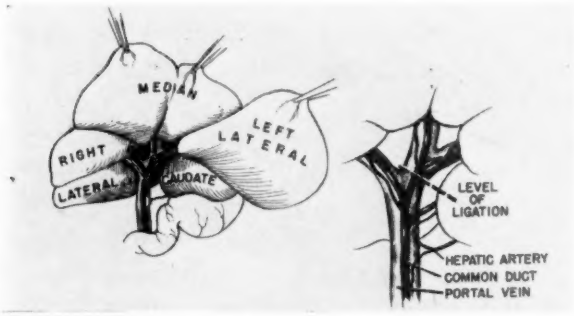

Fig. 1.—Hilar structures supplying the left and median lobes and sites of ligations performed.

Fig. 1 demonstrates the sites of ligation in these various groups. The structures in the hilum were arranged anatomically in such a way as to make accurate ligations of structures to left and median lobes quite feasible.

Dissection of the structures described was performed by isolation with a probe and double ligations performed with fine silk. In Groups C and D care was taken to preserve the minute hepatic arterial branches to the left and median lobes. Approximately equal numbers of rats from each group were operated upon at each session. Following surgery, 20 per cent glucose solution was substituted for their drinking water for 24 hours.

*Purina Laboratory Chow, Ralston Purina Co., St. Louis.

Four weeks following surgery, approximately two-thirds of each group of rats were sacrificed by exsanguination under light ether anesthesia. The left and median lobes of the liver, when present, were dissected free of the remaining liver and weight of the total liver as well as its components was obtained. Specimens were also fixed in 10 per cent formalin for histologic study. In order to be certain that changes induced by the surgery described were complete in 4 weeks, the remaining rats were not sacrificed until 8 weeks following operation. The procedure with this smaller group was identical with that employed in the 4-week group.

The body weights of the rats were obtained before surgery and at time of sacrifice. The ratios of total liver weight to body weight at time of sacrifice and the ratios of the weights of the remaining lobes (or surgically "unmanipulated" liver) to body weight were calculated. These ratios were compared with the ratios found in the control group to determine the degree of regeneration or restoration produced by these various alterations in anatomy. The validity of the mean values for these individual groups was determined by calculating the 95 per cent confidence limits for each of these means. When these limits did not overlap for any two given groups, the difference between the groups was statistically significant at the 5 per cent level.

RESULTS

The operative survivors in all groups continued to gain weight until the time of sacrifice. Comparison of mean body weights of each group before surgery and at time of sacrifice demonstrated similar mean weights and weight gains for each group (Table II). At the time of sacrifice the gross findings of the various groups were as follows: (A) In the control group, no deviation from normal rat liver anatomy was seen. (B) In those that had partial hepatectomy, the remaining lobes were hypertrophied, and the total liver mass appeared normal. (C) In those that had hepatic duct ligation, the relative size of the various lobes appeared normal grossly. The parenchyma of the lobes with obstruction of the biliary system was grossly indistinguishable from the

TABLE II. BODY WEIGHTS OF RATS OF ALL GROUPS IN GRAMS PRIOR TO OPERATION AND AT TIME OF SACRIFICE

GROUP	NUMBER OF RATS	INITIAL MEAN BODY WEIGHT (GM.)	MEAN BODY WEIGHT AT SACRIFICE (GM.)	MEAN BODY WEIGHT GAIN (GM.)		
				4 WEEKS	8 WEEKS	TOTAL GROUP
A. Controls	70	170	264			94
B. Partial hepatectomy	40	175	269	44	140	94
C. Hepatic duct ligation	48	186	265	48	133	79
D. Portal branch ligation	45	176	262	55	128	86
E. Combined arterial and portal branch ligation	25	170	263	55	134	93

remaining liver. (D) In those with portal branch ligation, the left and median lobes were distinguished by their characteristic shapes, but they were very small, thin, and darker in color than the remaining liver. The remaining liver was hypertrophied, lighter in color, and assumed the major portion of the liver mass. Total liver mass appeared normal. (E) In those with ligation of both arterial and portal venous supply to the left and median lobes, the remaining liver was quite similar to that seen after partial hepatectomy. The left and median lobes were always completely necrotic. The healthy-appearing rats that survived operation had all walled off these necrotic lobes by a fibrous shell. The gross appearance of the lobe structure of typical examples from these groups is seen in Figs. 2, 3, and 4.

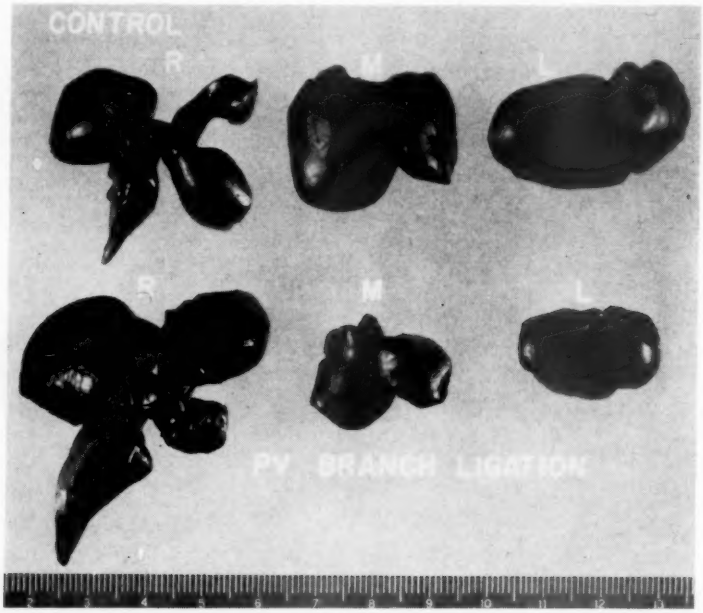

Fig. 2.—Autopsy specimens of livers of control rat (*above*) and rat subjected to ligation of portal supply to left and median lobes (*below*) 4 weeks after operation.

Although all data was calculated from animals surviving until time of elective sacrifice, the postoperative mortality was of some interest. For all animals in Groups A through D, the postoperative mortality was 16 per cent. Practically all of these deaths occurred in the first 18 hours. In Group E, with complete vascular occlusion to the left and median lobes, the postoperative mortality was 43 per cent and autopsy always revealed complete necrosis of these two lobes.

LIVER WEIGHT STUDIES

Controls.—The relationship between liver weight and body weight of the 70 control rats is shown graphically in Fig. 5. There was moderate variation as shown by the spread of individual observations. There was not a true linear relationship between these two variables as shown by failure of the projection of the regression line to pass through the zero point. Within a limited weight range, however, the liver/body weight ratio appeared to be a convenient and

valid expression for comparing liver size in the various groups. This ratio for the control series was 3.28 per cent. Excluding the left and median lobes, the mean ratio for the remaining liver/body weight was 1.06 per cent.

Total Liver Weights in Groups B, C, and D.—Fig. 6 compares the mean liver/body weight ratios of the experimental groups 4 weeks after operation with

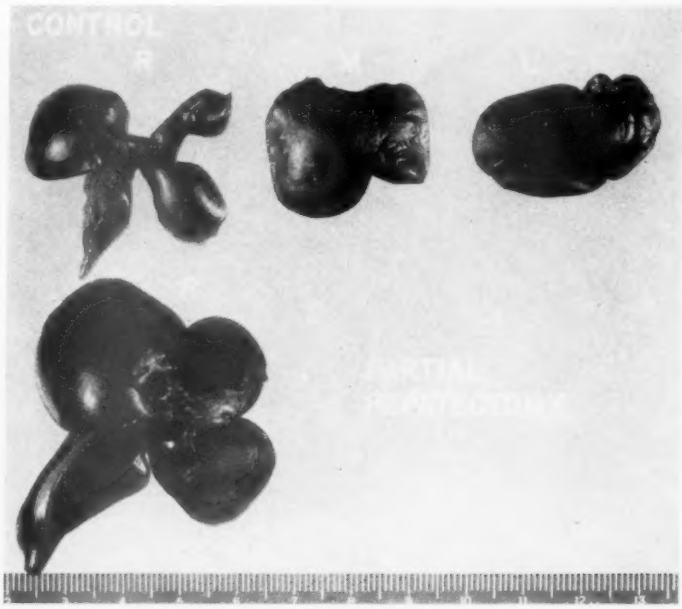

Fig. 3.—Autopsy specimens of livers of control rat (*above*) and rat subjected to removal of left and median lobes (*below*), 4 weeks after operation.

Fig. 4.—Autopsy specimens of liver of control rat (*above*) and rat subjected to complete vascular occlusion to left and median lobes (*below*) 4 weeks after operation. Note necrotic devascularized lobes.

the same ratio for the control rats. It is apparent that final liver weight in all groups closely approximated the expected liver weight of the normal rat, demonstrating no statistically significant differences among the groups. The

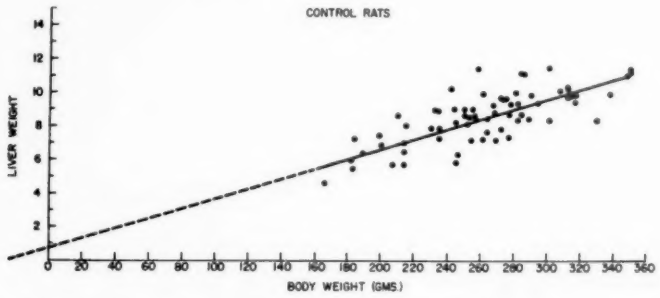

Fig. 5.—Relationship between liver weight and body weight at time of sacrifice (control rats).

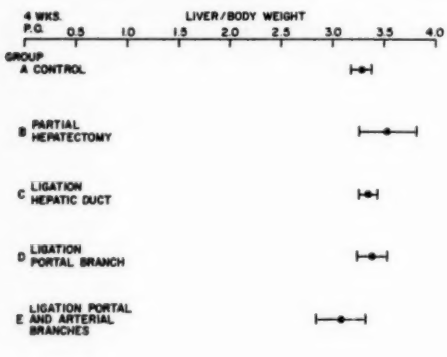

Fig. 6.

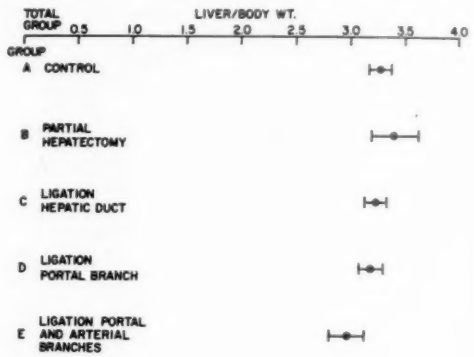

Fig. 7.

Fig. 6.—Total liver weight/body weight mean ratios (as per cent) with 95 per cent confidence limits (4 weeks postoperative).

Fig. 7.—Total liver/body weight mean ratios (as per cent) with 95 per cent confidence limits (4 and 8 weeks postoperative).

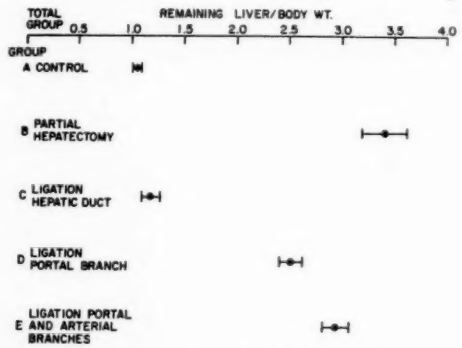

Fig. 8.—Remaining liver/body weight mean ratios (as per cent) with 95 per cent confidence limits (4 and 8 weeks postoperative).

data for the groups sacrificed 8 weeks after surgery do not affect this finding as shown by Fig. 7, which includes both the 4- and 8-week groups. Apparently any changes in total liver size were complete by 4 weeks.

Change in the Remaining Liver.—When the change in weight of the remaining or unmanipulated liver was evaluated following these various alterations in

the left and median liver lobes, the findings were much different. The data of the 4- and 8-week groups produced identical graphs and the mean ratios for the total group are shown in Fig. 8. Ligation of the hepatic duct to these two lobes produced little change in weight in the remaining liver, but the mean ratio of remaining liver/body weight was slightly greater than in the normal rats. The other procedures all produced marked differences in the remaining liver. As expected, there was a marked effort to restore liver after partial liver removal. Almost as intense restorative response occurred in rats with all vascular supply to a portion of the liver occluded. Ligating only the portal blood supply to these lobes produced marked atrophy of the corresponding liver and definite increase in the size of the remaining liver. There was, however, significantly less hypertrophy than in the group subjected to removal of the corresponding lobes.

HISTOLOGIC FINDINGS

The microscopic sections revealed normal hepatic architecture in Group A (controls). After hepatic duct ligation, the left and median lobes appeared almost normal despite minimal dilatation of the ductal system, but the remaining liver was normal histologically. After ligation of the portal blood supply, the left and median lobes had some atrophy, but the remaining liver appeared microscopically normal. The remaining liver, after excision of left and median lobes, appeared normal microscopically, as was the case in the residual liver after complete vascular occlusion of the left and median lobes (Group E). These two lobes were uniformly necrotic.

DISCUSSION

The complete restoration of liver mass after partial hepatectomy has been well established by many previous investigators. These experiments were performed for comparison with other procedures intended to produce a similar regenerative response. We required an animal that could tolerate each of several procedures. The findings following ligation of portal venous supply or hepatic duct were observed in rabbits which unfortunately do not tolerate large partial resections.[11] The observations following partial hepatectomy were made mainly in rats, fowl, and dogs. It was also necessary to use a species that could be operated upon in adequate numbers to make a comparative statistical study of the regeneration produced. The rat met these requirements satisfactorily.

Previous studies of the nature of the hypertrophied parenchyma after partial hepatic resection have strongly suggested that it was normal functioning tissue. The histologic appearance of this hepatic tissue has been considered normal. In this study the same held true for the portion of the liver considered remaining or unmanipulated liver, even if ligations of duct or vessels to another portion of the liver were carried out. On this basis, the ratio of the liver or a portion of liver to body weight has been utilized as a measure of liver restoration. Although the ratio of liver weight to body weight of control rats was not strictly linear, the means of the body weights in these groups were so close that the ratios described could be used as a valid measure of liver size.

Since the regenerative response produced by partial removal of the liver has been attributed to the resulting increase in portal pressure following such operations, our findings after portal ligation to these same lobes were of great interest. If the increase in size of the remaining liver was due entirely to changes in distribution of flow in the portal system, the portal ligation to these same lobes should have produced an identical response in the remaining liver as that following partial hepatectomy. The data on liver weight and liver-body weight ratios showed that this was definitely not the case (Fig. 8). Although intense regenerative response occurred following portal branch ligation, it fell short of that achieved by removal of these two lobes. Complete destruction of these two lobes by eliminating the remaining vascular supply, as in Group E, resulted in a regenerative response more like that seen following excision of these lobes. These data suggest that mechanisms in addition to vascular pressure phenomena must also be responsible for the liver growth produced by partial removal of the liver.

In view of the observations in rabbits concerning increase in liver mass after ligation of an hepatic duct,[12] our observations were somewhat surprising. Although slight atrophy of the lobes with ligated ducts did occur, the alteration was barely perceptible, except by statistical analysis. In the rabbit the rate of biliary flow in relation to size is 6 or 7 times that seen in many other animals, such as dogs, cats, rats, and possibly humans. Rous and Larimore[11] described a very dilated intrahepatic biliary tree following hepatic duct ligation in rabbits, and this was so great as to compress and occlude the portal venous system. The increase in liver size following hepatic duct ligation may have been mediated through the secondary effect of portal venous occlusion.

The rate of bile flow in terms of total body weight in the human is more analogous to the flows observed in rats than the large flows that have been observed in rabbits. This seems significant in light of the reports[1, 12] encouraging ligation of hepatic ducts to induce regenerative hypertrophy in the remaining liver of cirrhotic patients. Although such clinical trials were encouraged by the initial findings in rabbits, there has been no substantial evidence of benefit from these procedures and these data in the rat suggest that there is no definite physiologic basis for such operations.

SUMMARY

A comparative study was made of the degree of liver restoration in the rat after performance of each of the following procedures to the left lateral and median lobes of the liver: (1) excision (partial hepatectomy), (2) hepatic duct ligation, (3) portal branch ligation, and, (4) occlusion of arterial and portal blood supply. The degree of restoration present at the time of sacrifice was determined by the weights of the remaining lobes and their relationship to body weight. Histologic studies were also performed.

All groups at sacrifice had average total liver weight/body weight ratios in the same range as the controls. The rats subjected to hepatic duct ligation had minimal atrophy of the corresponding lobes and little increase in the remainder of the liver. Occlusion of portal blood flow to the two main lobes

produced marked atrophy of these lobes with corresponding hypertrophy of the remainder of the liver. Partial hepatectomy produced the greatest response. Occlusion of both arterial and portal blood supply to these same lobes produced necrosis of corresponding liver and the restorative response in the remaining liver was of the same order of magnitude as that following partial hepatectomy.

From these findings the clinical trial of hepatic duct ligation in cirrhotic patients to produce liver growth stimulation seems unwarranted. The hypertrophy of liver produced by ligation of a portion of the portal flow seems worthy of further investigation. This study suggests that hypertrophy of residual liver following partial hepatectomy in rats cannot be attributed entirely to increase in portal flow or pressure as has been claimed.

We wish to acknowledge the advice and encouragement of Drs. Parker Vanamee and H. T. Randall. We are also indebted to Dr. Irwin J. Bross for advice regarding statistical analysis and to Dr. Charles Berman for review of the histologic material. R. Barters, S. Denecko, and A. Khentigan gave invaluable technical assistance.

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GRANULOMAS AND SINUSES SECONDARY TO PERMANENT IMPLANTATION OF BRAIDED WIRE ALLOY SUTURES IN TISSUES

A Clinical Report

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IN RECENT years the use of stainless alloy wire has become very popular and has been used almost everywhere that catgut, silk, or cotton was formerly used. In the report by Babcock,[1] in 1947, it was used in operations on hernias, intestinal fistulas, abdominal walls, bile ducts, pancreas, rectal and gynecological operations, cleft lips and palates, and even upon the eye. The wire which was used was of varying sizes of monofilament wire which is made up of 18 to 20 per cent chromium, 8 to 10 per cent nickel, and 70 to 74 per cent steel. Babcock stated that "living tissues are non-reactive to embedded alloy steel wire." In many secondary operations, wire sutures removed after many years were found without fibrous encapsulation or other tissue reaction or staining and with the same bright shining surface as when introduced. Koontz and Kimberly[4] state that there was "possibly slight irritation from a stainless steel suture that caused a reaction immediately adjacent to it. . . ." This was not present when tantalum wire was used. Gerard[2] states that Wu and Pai found a slight infiltration of round cells, fibroblasts, and a few plasma cells in the region of the sutures after 5 days. Catgut and other sutures showed much more reaction. Trimpi and Bacon[5] advise the use of figure-of-eight sutures including fascia, muscle, and peritoneum and report no ill effects due to the formation of sinuses and abscesses, among others. We originally used the monofilament wire sutures, suggested in the literature just described, in those cases in which we felt there might be a tendency to heal poorly or in obese patients. Our only complaint, the same as that reported in the literature, was of painful wounds in thin people, occasionally necessitating the removal of sutures.

In recent years, braided steel alloy wire has been used by us and from a technical viewpoint has been completely satisfactory. We have used it in place of the single wire sutures and found that it handles almost as well as silk or cotton. According to the brochure and references cited by the manufacturers this has the same qualities in the tissues ascribed to the single filament wires. Recently we have been disturbed by the presence of persistent small areas of drainage from the wounds which could not be cleared up until the wire sutures were removed.

Received for publication Oct. 25, 1958.

CASE REPORTS

CASE 1.—L. J., a 49-year-old white man, had had a subtotal gastrectomy for duodenal ulcer in December, 1957. On the sixth day he complained of pain in the wound during a spell of persistent coughing. He felt that something had broken loose. The wound looked normal but, on removal of a skin stitch, a considerable amount of serosanguineous fluid was evacuated. The wound healed without further trouble but, as expected, a hernia developed during the next 2 months. Three small draining areas developed which persisted for several months until the braided wire was removed. There was no sign of gross infection in the wound at any time.

CASE 2.—In October, 1957, E. G., a 63-year-old white woman with arthritis, who had been treated with cortisone, was admitted to the hospital with a marked peritonitis of unknown origin. It was believed to be due to perforation of the colon due to the use of the drug. The symptoms subsided completely and a barium enema showed two polyps in the sigmoid. Sigmoidoscopic examination was negative. An exploratory operation was performed and the polyps removed. She was seen 2 months after the original operation complaining of drainage from the wound and, on probing, several wire sutures were found and removed, resulting in complete healing. She has developed an incisional hernia.

CASE 3.—This 21-year-old white boy had had a colectomy and ileostomy in August, 1957, for ulcerative colitis followed by intestinal obstruction of the small bowel for which he was operated upon. The wound was infected, but was clean and healed before discharge. Abdominoperineal removal of the lower sigmoid colon and rectum was done at a third stage. Convalescence was uneventful except for the persistence of several draining sinuses which appeared 2 months later in the original incision and which did not heal until the underlying braided wire sutures were removed. In July, 1958, two other wires were removed. No hernia is present in either the original or second incision.

CASE 4.—A 42-year-old white man was admitted to the hospital on Aug. 1, 1957, for an acute severe pancreatitis which was treated by medical therapy, Wangensteen suction, intravenous fluids, and so forth. After 2 weeks, a gall bladder visualization was done which did not show the gall bladder as expected. We felt that in view of the fact that he was a laborer and also might not follow a diet exactly, it would be worth while to perform a transduodenal sphincterotomy. At operation, the gall bladder was distended but otherwise normal. The pancreas was markedly enlarged throughout its entire length, but there were no signs of fat necrosis. A sphincterotomy and cholecystectomy were done. The incision was closed with figure-of-eight braided wire through fascia, muscle, and peritoneum. He had a stormy convalescence marked by signs which we considered was a recurrent pancreatitis. A hernia developed in the wound and there were constant attacks of pain also which seemed almost as bad as the original complaint. He was repeatedly seen and the presence of a mass which was growing slowly was noticed in the hernia area. This was definitely diagnosed as a pancreatic cyst but, since the symptoms subsided, the patient was allowed to return to work with the hope that this might possibly absorb. Despite the fact that he felt well, the mass became so large that he returned to the hospital May 8, 1958, for a pancreaticogastrostomy. At operation, the old scar was dissected free from the underlying tissue. Upon exposing the upper part of the wound, a mass the size of an olive was found which at first was thought to be the ensiform. On examination, however, it was found to be a hard encapsulated mass which was attached to the tip of the ensiform. This was removed completely. On cutting this mass, a wire suture was found in the center (Figs. 1 and 2). As the dissection progressed, many hard fibrous tumors were found in the lateral edge of the fascia. These were opened and, in each case, a granulomatous mass was present in the center which was necrotic tissue surrounding a braided wire suture. The pathologic report was, "granuloma due foreign body reaction." Despite the trouble described, the hernia was repaired by steel wire mesh and the wound was healed and clean when last seen on July 19, 1958.

Comment.—In reviewing the article by Babcock,[1] we noted that although, as far as we could determine, he did not use braided wire in his experiments, he stated that "stranded wire from its capillarity would seem to have a greater tendency to carry or hold infection than the plain wire although much less than that of catgut, silk, or cotton." Howkins and Hans,[3] in

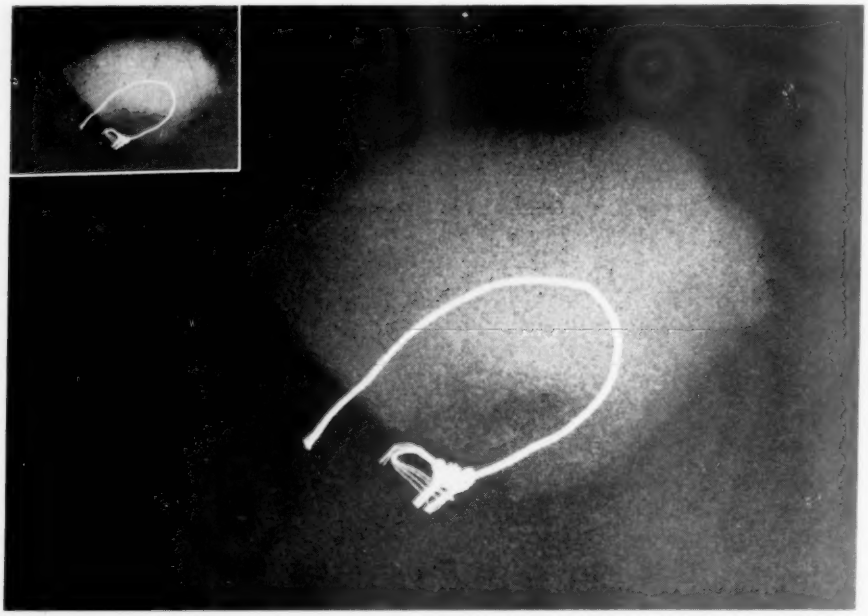

Fig. 1.—Roentgenogram of granuloma removed from Case 4 (insert is actual size). Enlargement of tumor and 3-0 braided wire shows the separate strands of wire.

Fig. 2.—A low-power photomicrograph of granuloma seen in Fig. 1. The opening is small indentation of space formerly occupied by braided wire shown in Fig. 1.

1952, state that they had been employing stainless steel wire for the closure of abdominal wounds for many years with complete satisfaction. Because of its tendency to kink and break subsequently, they decided to try braided tantalum wire because of its flexibility

and ease in handling. They state that it was used at four hospitals for some months until they noticed that, in 136 cases of midline subumbilical incisions, there were 9 herniations and 11 infections with 6 of the 11 infections requiring removal of the wire before the abscess and sinuses cleared up.

In 1950, Koontz and Kimberly[3] had stated that "braided tantalum wire is resistant to infection in spite of the interstices occasioned by the braiding which might be considered possible sites of infection."

CASE 5.—This patient, a 47-year-old white woman, was operated upon in May, 1957, through a right rectus incision for repeated attacks of gallstones for which she had had two previous cholecystostomies. At operation, the liver, duodenum, and colon were fused, necessitating sharp dissection before the anatomy could be demonstrated. A shrunken gall bladder, consisting of what seemed to be two separate pockets with stones in each, was found and removed and the common duct drained. No stones were found in the common duct, and subsequent radiographic visualization of the duct through the T-tube showed a normal biliary tree. Convalescence was uneventful and the T-tube was removed on the tenth day. She returned in June, 1958, with the complaint that she had been having severe pain in the incision and felt a small lump. Examination showed an irregular mass the size of a walnut deep in the wound and apparently fixed to the fascia. There was no impulse on coughing, but the patient complained of pain when she did so. Fortified by our knowledge of the reaction of tissues to braided wire, we made a diagnosis of granuloma and explored the wound on June 12, 1958. As expected, the typical sign of a cartilaginous mass, the size of a walnut, and fused with the fascia, was found. Its removal showed the presence of steel wire and a typical granuloma tissue reaction. Culture of the granuloma showed no organism. On removal of the wire, the area healed promptly.

CASE 6.—A 39-year-old white woman had had a cholecystectomy performed on Aug. 28, 1957, through a right rectus incision which was closed with a figure-of-eight suture of 3-0 braided wire. Drainage was through a stab wound. Convalescence was uneventful. On Oct. 23, 1957, she complained of tenderness in the mid-portion of the incision. A small amount of serum was evacuated. The area was probed for a wire suture but none was found. The wound healed promptly. On July 13, 1958, she was delivered of a full-term baby. Postpartum, a lump, the size of a golf ball, was noted in the incision and was located on the right side of the previous drainage area. It was raised and nontender. This was excised July 21, 1958, and was found to contain a wire suture surrounded by a typical granuloma reaction. A moderate amount of pus was present and a culture was taken. The report was "hemolytic *Staphylococcus aureus* coagulase positive." She had not received antibiotics during the postoperative period.

DISCUSSION

As far as we know this condition has not been reported to date and the suggestion by Babcock[1] of the possibility of trouble from braided wire has not been substantiated clinically. The clinical report by the British surgeons of trouble caused by braided tantalum wire contradicts the experimental report by Koontz and Kimberly.[4] In their cases, as well as ours, the operations performed were always through vertical incisions and, in our cases, all were potentially infected as well as being major in character. No. 3-0 wire was used in all cases. We took cultures of the granuloma in the case which occurred approximately 13 months after complete healing and found no organism present. Case 6, however, showed a *Staphylococcus aureus* infection. In 3 cases, a hernia developed in the wound and, as in Case 4, the wire sutures probably cut through one side, suggesting either that the suturing was too

tight or that too small a bite was taken on one side. Except in Case 6, the use of antibiotics probably masked the real condition and would seem to bear out Babcock's hypothesis of prolonging the infection.

During the past 3 years we have used 3-0 braided wire as permanent figure-of-eight sutures through fascia, muscle, and peritoneum in 118 patients with vertical incisions (Table I). We used this in patients whom we considered probable candidates for dehiscence due either to obesity, type of operation, condition of the tissues, or general debility. Except for those cases reported, healing was uneventful and none of the wires had to be removed. This would rule out braided wire as causing granulomas or sinuses unless some other factor such as infection and/or necrosis if tissues is present. This is also borne out by normal healing of sutures in draining wounds outside of the discharging area.

TABLE I. ABDOMINAL VERTICAL INCISIONS CLOSED BY FIGURE-OF-EIGHT BRAIDED WIRE SUTURES THROUGH FASCIA, MUSCLE, AND PERITONEUM, 1955-1957

PROCEDURE	NUMBER OF CASES	POSTOPERATIVE SINUSES OR GRANULOMAS NECESSITATING REMOVAL OF WIRE	POSTOPERATIVE HERNIA
Biliary tract (gall bladder and common duct)	46	2	1
Gastric	32	1	1
Intestinal resection (including colon)	30	2	0
Pancreatic	3	1	1
Abdominal exploratory	2	0	0
Hiatus hernia (abdominal)	1	0	0
Ventral hernia	3	0	0
Totals	117	6	3

SUMMARY

1. A survey of the use of monofilament and braided wire sutures, both experimentally and clinically, has been presented.

2. Braided steel alloy wire used as permanent sutures tends to cause granulomas and sinuses in the presence of infection and/or necrosis of tissues.

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PRODUCTION OF ACUTE HEMORRHAGIC PANCREATITIS IN DOGS BY MEANS OF AN EPISODE OF INTRAVASCULAR CLOTTING IN THE PANCREAS

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DURING the course of experiments designed to produce lower nephron nephrosis in dogs,[4-10] it was noted that some of the dogs had acute hemorrhagic pancreatitis at autopsy. These experiments had shown the following: (1) The intravenous injection of incompatible (human) blood into dogs results in disseminated intravascular coagulation, predominantly in the lungs but also in the liver, pancreas, kidneys, and bowel mucosa.[8] (2) The intra-aortic injection of incompatible (human) blood also results in disseminated intravascular clotting predominantly in the abdominal viscera, but also in the lungs.[9] The thrombi formed quickly and might disappear quickly. Under different experimental conditions, thrombi persisted in different locations. The organ or organs through which the coagulating blood circulated first received and retained the majority of the thrombi.

It was found[9] that the performance of a laparotomy and kidney biopsies, greatly facilitated the formation of the abdominal thrombi particularly in the bowel mucosa.[5] The freeing up of one kidney greatly facilitated the formation of thrombi in the opposite kidney.[4, 10] The temporary occlusion of the superior mesenteric artery during the transfusion largely prevented the bowel lesions which otherwise had proved fatal.[4, 6, 10] Small quantities of transfused blood seemed to produce both capillary and arterial thrombosis, while larger quantities of blood produced only capillary thrombosis.[4] The syndromes of shock, both reversible[7] and irreversible,[6] lower nephron nephrosis,[4, 10] and pesudomembranous enterocolitis[5, 11] were produced in various situations in these experiments depending upon the localization of the thrombi.

It is the purpose of this paper to show that acute hemorrhagic pancreatitis can be produced by intravascular clotting in the pancreas.

MATERIALS AND METHODS

Ninety mongrel dogs were anesthetized with sodium pentobarbital, a laparotomy was performed, and the left kidney freed from its bed. Both femoral arteries were isolated and a polyethylene catheter was inserted in each

Received for publication Oct. 3, 1958.

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until its tip reached the level of the diaphragm. One was used for blood pressure studies.[7] The other was used for the injection of incompatible (human) blood. The superior mesenteric artery was temporarily occluded during the injection of incompatible blood. Kidney biopsies were taken at 15, 30, 60, and 120 minutes, and at 3 hours the left kidney was removed. Several variations of the experiment were performed.[4, 10] In Group A (11 dogs) the left kidney was freed from its bed before transfusion was given. Four cubic centimeters of human blood per pound of dog was used. In Group B (15 dogs) the kidney was also freed from its bed before the transfusion, but only 1 c.c. of blood per pound of dog was used. In all groups the length of the injection was the same (5 to 10 minutes). In the remaining dogs (Group C, 64 dogs) various additional procedures were carried out.[4] However, all the rest of the dogs were given 4 c.c. of human blood per pound of dog and the left kidney was not freed from its bed until after the transfusion.

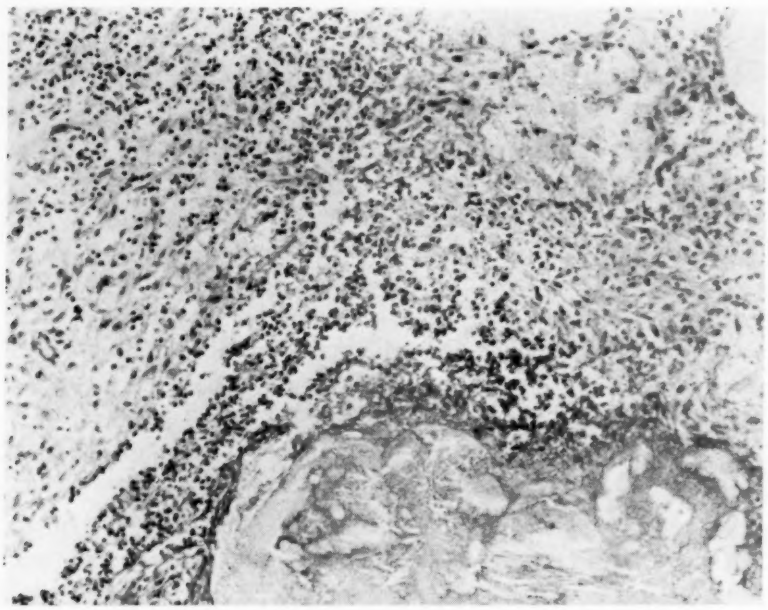

Fig. 1.—Section of dog pancreas showing almost total destruction of normal pancreatitic tissue, inflammatory reaction, and fat necrosis.

RESULTS

Group A.—Of the 11 dogs, 6 died in uremia after several days of anuria. Two others also were anuric for several days but then started to excrete urine. All 8 of these dogs showed the pathologic picture of lower nephron nephrosis at autopsy and one showed microscopic evidence of acute pancreatitis. Of the remaining 3 dogs, one died in less than 24 hours and 2 survived with few symptoms.

Group B.—Of the 15 dogs, 8 died within 24 hours, 2 died in uremia and lower nephron nephrosis, and 5 survived. Three dogs showed acute hemorrhagic necrosis of the pancreas with fat necrosis. (Figs. 1, 2, and 3.)

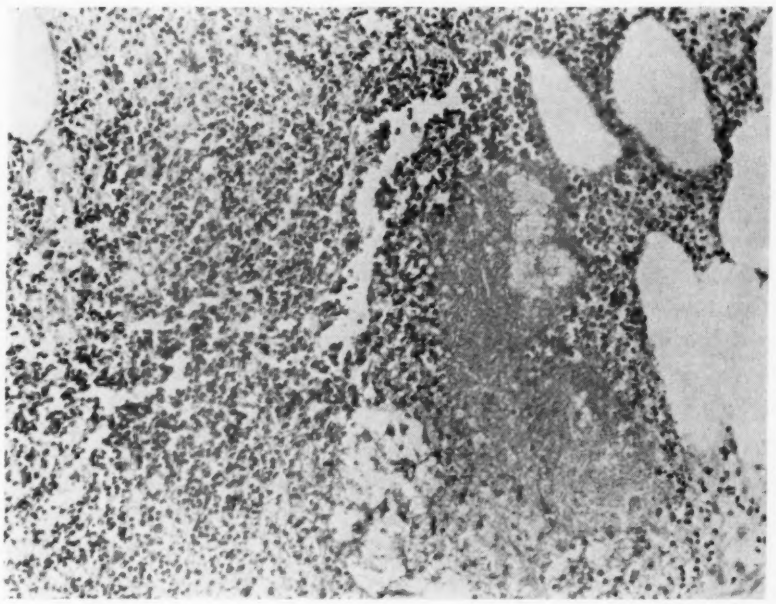

Fig. 2.—Section of dog pancreas showing complete destruction of normal pancreatitic tissue, inflammatory reaction, and fat necrosis.

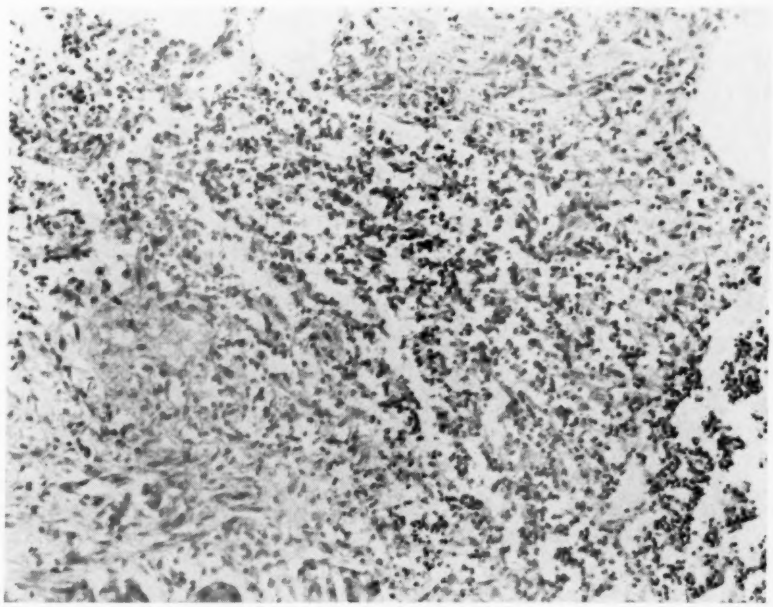

Fig. 3.—Section of dog pancreas showing nearly complete destruction of pancreatitic tissue. An acinus is visible in the lower left. There is inflammatory reaction and fat necrosis.

Group C.—Of the 64 other dogs, only one showed evidence of acute hemorrhagic pancreatitis at autopsy. None had renal failure.

DISCUSSION

Thal and associates[13] produced acute hemorrhagic pancreatitis by a local Schwartzmann reaction. There was massive tissue destruction produced by the formation of intracapillary thrombi. In a morphologic study[14] of 42 cases of fatal acute pancreatitis, 83 per cent had thrombi in the veins or capillaries. Bernard[2] in describing the essential pathologic lesion characterizes it as a focal, aseptic, hemorrhagic necrosis. (This is the characteristic lesion caused by intracapillary thrombi in our experiments not only in the pancreas but in the liver, kidneys, and bowel.) Bernard also states that 50 to 70 per cent of cases have either lower nephron nephrosis clinically or by microscopic examination of the kidneys. Shock is characteristic. Both shock[6, 7] and lower nephron nephrosis[4, 10] are associated with the pancreatitis in the present experiments, both being a manifestation of intravascular coagulation. Ackerman[1] has described the simultaneous occurrence of acute pancreatitis and lower nephron nephrosis after incompatible transfusion. Similar combination of pancreatitis and lower nephron nephrosis have been noted after transurethral resection with a hemolytic reaction.[3]

The "common passage" mechanism of production of acute pancreatitis is undoubtedly responsible for many cases. However, 3 fatal cases of acute pancreatic necrosis seen at the U. S. Army Hospital, Fort Belvoir, Virginia, at the U. S. Army Hospital, Frankfurt, Germany, and U. S. Army Hospital, Fort Benning, Georgia, were carefully studied by meticulous dissection. In none of these cases was there either a common channel or any sign of ductile obstruction or biliary tract disease.

SUMMARY

1. It is possible to produce acute pancreatic necrosis in dogs by means of an intra-aortic injection of incompatible (human) blood.

2. This reaction is associated with an episode of intravascular clotting which occurs in the pancreas, as well as other organs.

3. Small quantities of incompatible blood are apparently more potent in causing pancreatic lesions than are larger quantities.

CONCLUSION

Intravascular thrombi in the pancreas will produce focal aseptic hemorrhagic necrosis and the pathologic picture of acute hemorrhagic pancreatitis.

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PAGET'S DISEASE OF THE BREAST

A Twenty-Year Survey of Cases Presenting at a Large General Hospital

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INTRODUCTORY STATEMENTS

PAGET'S disease is an uncommon form of breast carcinoma that generally arises in the main excretory ducts of the breast, and extends to involve the skin of the nipple and areola. The skin lesion is of low-grade malignancy. There is frequently an eczematoid change in the nipple or areola and for this reason, Paget's disease was originally considered to be an inflammatory lesion. The lesion may precede an obvious carcinoma by many years.

Velpeau[10] first described this condition in 1841, but was unaware of the frequent association of carcinoma with the nipple lesion, which was first recorded by Sir James Paget[7] in 1874. Butlin[3] soon thereafter recorded the microscopic features of this disease, although the Paget cell had been described earlier by Darier.[4] Jacobaeus[5] and Muir[2, 6] drew attention to the frequent association of Paget's disease with intraductal carcinoma. However, we have observed that other types of breast cancer may promote a similar reaction. Of the 21 patients reviewed in this series, 3 presented with a frank scirrhous carcinoma and one was noted to have a carcinoma of the medullary type.

PATHOLOGY

The gross features of Paget's disease may vary. The most striking characteristic is the eczematoid and usually well-defined superficial ulceration of the nipple and areola. The skin is erythematous, granular, florid, and oozing, or it may be covered by fine scales. The central portion of the lesion is surrounded by a less well-defined area of hyperemia and edema. Secondary bacterial infection may cause a local suppurative necrosis which may mask the eczematoid changes.

Microscopic examination reveals hypertrophy of the epidermis and a downgrowth of rete pegs. The characteristic histopathologic feature is the presence of large, clear, vacuolated cells with small, pyknotic nuclei, known as Paget's cells. They occur singly or in groups, and are most frequently found in the basal layer of the epidermis.[1] The underlying dermis shows

Received for publication Nov. 8, 1958.

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infiltration with lymphocytes and plasma cells. The elastica becomes hyperplastic and later undergoes hyalinization and secondary basophilic degeneration of connective tissue. As the disease progresses, a gradual thinning of the superficial epidermis occurs which may disappear entirely. In addition to these changes, other histologic features of intraductal carcinoma are usually present.

In this series, we were impressed by the failure of the pathologic changes to reflect the biologic activities of the underlying tumor. It was impossible to speculate as to the prognosis or the optimum method of management in the individual case on the basis of the presenting histology.

CLINICAL FEATURES

This disease occurs more frequently in women but occasionally has been reported in men.[8, 9, 11]

An early diagnosis of Paget's disease is possible because of the external manifestations of the lesion, of which the eczematoid response is the most outstanding. Ten of the patients in this series had an eczematoid or ulcerative lesion of the nipple for 6 months or longer before the diagnosis of breast carcinoma was made. Too frequently, this lesion is mistaken for a benign form of eczema or contact dermatitis, and is ignored or treated with topical medications for months or even years. One patient in the present series was so treated for 17 years prior to the discovery of the true pathology.

A sensation of itching or burning about the nipple is often the first symptom of Paget's disease. The lesion may present itself as an erythematous, oozing, dermatitis or it may be dry and scaly. There is frequently a copious, clear yellow discharge from the nipple. Following the eczematoid stage, the discharge from the nipple may become bloody. Four of our patients presented themselves for examination only when a bloody discharge was noted.

The nipple may be hypertrophied as seen in one of our cases, eroded as noted in 2, or retracted. Usually the lesion is circumscribed and confined to the nipple and areola, but occasionally it extends to involve the skin of the breast.

Frequently no mass can be palpated in the breast. When present, it is generally located directly beneath the nipple. Four patients in this series presented themselves with such a finding. In 3 others an unsuspected mass was found on clinical examination. Subsequently, however, a carcinoma was found in all those patients who were operated upon.

On the basis of the clinical examination, axillary nodes were discovered in only one patient and this only in the presence of advanced disease. This suggests that the nipple lesion occurs early in the course of the disease, offering an opportunity for early diagnosis.

Most chronic erosions that involve the nipple epithelium of only one breast are malignant. Contact dermatitis usually occurs bilaterally and in younger individuals, whereas bilateral Paget's disease is extremely rare. The

TABLE I. CASES OF PAGET'S DISEASE OF THE BREAST ENCOUNTERED IN THE HAMILTON GENERAL HOSPITAL, HAMILTON, ONTARIO, BETWEEN THE YEARS 1937 AND 1957

NUMBER	AGE	SEX	PRESENTING FINDINGS	DURATION OF SYMPTOMS PRIOR TO DIAGNOSIS	MASS IN BREAST	AXILLARY NODES	PATHOLOGY	TREATMENT	FOLLOW-UP
1.	35	F	Ulceration of nipple	2 mo.	No	No	Intraductal carcinoma	Excision of nipple, radiation	Well 8 yr.
2.	54	F	Mass in breast	3 mo.	Yes	No	Scirrhous carcinoma	Radical mastectomy	Recurrence, 4 yr.; alive
3.	53	F	Eczema nipple	6 mo.	No	No	Scirrhous carcinoma	Radical mastectomy, radiation	—
4.	85	F	Eczema nipple	17 yr.	No	No	Squamous epithelioma changes compatible with Paget's disease	Biopsy	No change 1 yr.
5.	63	F	Hypertrophy of nipple	6 mo.	No	No	Intraductal carcinoma	Radical mastectomy	Well 18 mo.
6.	33	F	Eczema nipple; bloody discharge	6 mo.	No	No	Intraductal carcinoma	Radical mastectomy	Well 1 yr.
7.	47	F	Eczema nipple	8 mo.	No	No	Intraductal carcinoma	Radical mastectomy, radiation	Well 3 yr.
8.	70	F	Eczema nipple	6 mo.	No	No	Intraductal carcinoma	Radical mastectomy, radiation	Well 5 yr.
9.	51	F	Eczema nipple	6 mo.	No	No	Nipple showing evidence of Paget's disease	Excision of nipple	Well 2 yr.
10.	58	F	Eczema nipple	2 yr.	Yes	No	Medullary carcinoma	Radical mastectomy, radiation	Well 4 yr.
11.	41	F	Ulceration of nipple	1 mo.	No	No	Intraductal carcinoma	Simple mastectomy	Well 6 yr.
12.	66	F	Eczema nipple; bloody discharge	6 mo.	Yes	No	Intraductal carcinoma	Radical mastectomy, radiation	Well 6 yr.
13.	58	F	Eczema nipple; bloody discharge	12 mo.	No	No	Intraductal carcinoma	Simple mastectomy, radiation	Recurrence 5 yr.; dead 6 yr.

14.	33	F	Bloody discharge	6 mo.	No	No	Intraductal carcinoma	Simple mastectomy, radiation	Well 7 yr.
15.	44	F	Mass in breast	6 mo.	Yes	No	Intraductal carcinoma	Radical mastectomy, radiation	Recurrence 9 yr.; dead
16.	74	F	Bloody discharge	1 mo.	No	No	Intraductal carcinoma	Simple mastectomy, radiation	Well 12 yr.
17.	60	F	Eczema nipple	10 mo.	No	No	Intraductal carcinoma	Simple mastectomy	Well 13 yr.
18.	70	F	Eczema nipple	6 wk.	No	No	Intraductal carcinoma	Simple mastectomy	Recurrence 3 yr.
19.	25	F	Eczema nipple	4 mo.	Yes	No	Intraductal carcinoma	Radical mastectomy	Recurrence 1 yr.; dead
20.	48	F	Mass in breast	5 mo.	Yes	Yes	Scirrhous carcinoma	Excision of nipple	Recurrence 4 mo.; dead
21.	73	F	Mass in breast	7 mo.	Yes	No	Intraductal carcinoma	Simple mastectomy	Well 2 yr.

TABLE II. DURATION OF SYMPTOMS PRIOR TO DIAGNOSIS

SYMPTOMS	UNDER 6 MO.	6 MO.-1 YR.	OVER 1 YR.	TOTAL CASES
Eczema or ulceration of nipple	4	8	2	14
Bloody discharge of the nipple	1	4	0	5
Palpable mass in the breast	2	2	0	4
Hypertrophy of the nipple	0	1	0	1

eczematous surface of a benign lesion is usually soft and pliable and the margin of the lesion exhibits no induration on palpation. The lesion in Paget's disease is rigid, and its edges are hard and abrupt. Benign lesions rarely destroy the nipple. Every lesion of the nipple or areola should be biopsied when there is doubt as to the diagnosis. Lesions that do not respond to conservative therapy within 2 weeks should be biopsied.

TREATMENT

An accurate and early diagnosis is the prerequisite to rational treatment and to a favorable prognosis. The diagnosis should be based upon an accurate history, careful physical examination, and in most cases a biopsy of the lesion.

The treatment of Paget's disease of the breast is essentially the treatment of breast carcinoma. Local excision of the nipple is not indicated except as a biopsy procedure. Superficial radiation will frequently improve the skin lesion, but ignores the associated carcinoma. The relative merit of simple or radical mastectomy with or without pre- or postoperative radiation has not been definitely settled. The choice of therapy depends upon the stage of the tumor, the age and general condition of the patient, the biologic relationship between host and tumor (insofar as this can be judged), and the skill of the surgeon and the facilities for radiotherapy that are available.

TABLE III. RESULTS OF TREATMENT

TYPE OF TREATMENT	NUMBER OF CASES	SURVIVING UNDER 5 YEARS		SURVIVING FROM 5 TO 10 YEARS		SURVIVING OVER 10 YEARS	
		NO RECURRENCE	RECURRENCE	NO RECURRENCE	RECURRENCE	NO RECURRENCE	RECURRENCE
Local excision	3	2	1				
Local excision and x-ray	1			1			
Simple mastoidectomy	4	1	1	1		1	
Simple mastoidectomy and x-ray	3		1	1		1	
Radical mastoidectomy	4	2	2				
Radical mastoidectomy and x-ray	5	2		2	1		
Total	20*	7	5	5	1	2	0

*One case was lost to follow-up.

DISCUSSION

It is difficult to draw concrete conclusions regarding therapy on the basis of this small series. We are, however, faced with the fact that the underlying pathology is that of a malignant change, and although we cannot predict this tumor's biologic activity in the individual case it seems only rational that this lesion should be managed in a similar manner as the neoplastic lesions of the breast not associated with a nipple lesion. In an effort to obtain a cure, it is our feeling that the time for radical surgery is prior to the extension of the disease to the regional lymph nodes. Once the disease has reached the regional nodes, the problem of adequate treatment becomes the same as we face in dealing with other forms of breast carcinoma because it is virtually impossible to tell how far the process has progressed beyond these confining limits. The prognosis in those cases showing positive axillary nodes becomes understandably guarded.

All the patients in this series were women between 25 and 85 years of age. The average age was 54 years. The majority of patients noted the presence of a lesion for 6 months or longer before a diagnosis was established. The most common finding was an eczematoid lesion of the nipple and areola (presenting symptom in 14 patients in this series). A mass was palpated in the breast in only 7 patients, but carcinoma was found in all who were operated upon, the only exceptions being Cases 4 and 9, the first of which was simply biopsied and the latter underwent only a superficial excision of the nipple. In neither specimen was sufficient tissue submitted to demonstrate an underlying tumor.

The possibility of the presence of an underlying carcinoma must be suspected in any case of unilateral eczema of the nipple which does not respond rapidly to local therapy, and must be ruled out by biopsy examination.

SUMMARY

Paget's disease of the breast is an uncommon disease. It has characteristic histopathologic features, and is usually found in association with an intraductal carcinoma of the breast. It generally appears as an eczematous lesion of the nipple or areola, and may be ignored or treated as a benign lesion for many months before the diagnosis is established. The salient features of 21 cases of Paget's disease of the breast encountered in a general hospital over a 20-year period are briefly presented.

We wish to thank Dr. Loyd S. Green, Director of the Hamilton Division of the Ontario Cancer Clinics, for his assistance and encouragement in compiling the material for this paper.

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EXTRAMAMMARY PAGET'S DISEASE

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CONTROVERSY still exists about the exact nature of Paget's disease of the nipple and extramammary sites. Some authors have considered the disease to be a type of primary malignant tumor peculiar to the skin, but others are quite convinced that Paget's disease, regardless of its location, always represents a process secondary to underlying primary carcinoma. The true pathogenesis of the condition is difficult to clarify since the phenomenon as it affects the skin is usually of long duration by the time diagnosis is established. Regardless of the present inability to solve the controversy, certain facts exist about extramammary Paget's disease.

Paget's disease arising in an extramammary area occurs most often in parts of the body where a generous supply of apocrine glands exists. Almost all of the reported cases of extramammary Paget's disease have been found in the axillae and perianal region. This suggests a close relationship between primary malignant disease of the apocrine glands and an associated intraepidermal cellular malignant spread. The literature, however, contains reports of several cases in which extramammary Paget's disease has occurred without an underlying malignant process. In certain instances it is possible that the underlying malignant growth was of such small size that it was completely overlooked even though a careful study had been made.[1]

Pinkus and Gould,[9] in a review of the problem, suggested that Paget's cells may be associated with an underlying rectal carcinoma. They called attention to the analogy between Paget's disease of the nipple with its underlying ductal carcinoma and Paget's disease of the perianal skin with its associated malignant tumor of the rectum. Green and Epstein[5] reported a case in 1950 in which no underlying rectal carcinoma was present. It is interesting to note that their patient had been diagnosed and treated as having perianal neurodermatitis for 7 years prior to surgical consultation.

Pearson and McArt[8] also believe that Paget's deposits are true carcinomatous cells and represent secondary intraepithelial metastases from primary glandular carcinoma. These authors presented a case of primary carcinoma of the apocrine glands in the anal region in which there were metastases throughout the body. Since their patient had widespread metastases along with the perianal Paget's phenomenon, they suggested that the process should be considered merely as one of primary carcinoma of the apocrine glands with a generalized spread through lymphatic pathways to distant sites and organs as well as to the overlying skin. As such, the process is identical with the well-known

Received for publication Sept. 29, 1958.

lymphatic spread of other types of tumors at other sites of origin. The picture is different only in that in these cases the intradermal metastases occur for some unknown reason as an unconventional mode of lymphatic spread to the skin. Still unexplained is the fact that unlike most malignant processes extending to the skin, ulceration is uncommon in Paget's disease.

There is less disagreement today regarding the nature of extramammary Paget's disease than there was just a decade ago. At that time a variety of opinions flourished and the varying conceptions of the problem are well demonstrated by the fact that although by 1937 more than 70 cases of extramammary Paget's disease had been reported in the world literature, Weiner[12] in reviewing most of them found only 15 cases which satisfied his criteria for a diagnosis of extramammary Paget's disease. Weiner noted that in each of the 15 cases Paget's disease of the skin occurred only in the external genitalia or axillae, and he was one of the first to suggest that extramammary Paget's disease represented intraepidermal metastases from carcinoma of the apocrine glands.

Subsequent authors have accepted Weiner's observations as valid.[2, 3, 4, 6] Stout[11] thought that extramammary Paget's disease consisted of lesions of the skin similar to those in Paget's disease of the nipple and that the disease was usually associated with underlying sweat-gland carcinoma and may be secondary to it. Parsons and Lohlein[7] state that in order to diagnose extramammary Paget's disease, carcinoma of the underlying sweat glands must be present. Most authors do not insist on the presence of carcinoma of the sweat glands to justify a diagnosis of extramammary Paget's disease.

The two cases reported here present additional evidence in support of the concept that Paget's phenomenon represents a mode of lymphatic spread of underlying malignant disease to an intraepidermal location. Dockerty and Pratt,[2] as well as Rabson and co-workers[10] have demonstrated the presence of mucoid material in the metastatic cells of the epidermis as well as in the underlying carcinoma and believe that this verifies the metastatic nature of the disease.

In the first case to be presented, mucoid adenocarcinoma of the anal mucosa coexisted with Paget's disease of the anus for a period of at least three years. The second case was proved to be of prostate-gland origin and the Paget's phenomenon in the skin of the left inguinal region merely represented part of a widespread generalized metastatic process.

CASE REPORTS

CASE 1.—A 55-year-old white man was admitted to the University of California Hospital, San Francisco, on Jan. 7, 1958. Three and one-half years before entry he had undergone a Whitehead operation for internal hemorrhoids. A portion of the removed tissue was studied microscopically and was considered to be entirely benign.

Two years prior to entry the patient noted a nontender firm mass in the left perianal region at the margin where the rectal mucosa had been sutured to the perianal skin. He did not seek medical attention until one year had passed, at which time the mass was electrocoagulated. No specimen was preserved for study at that time.

Six months before entry the patient first noted a white, plaquelike growth on the right side of the perianal region. The mass began to enlarge and became tender and friable.

The area was removed locally a few days prior to hospital entry. Pathologic examination showed the presence of adenocarcinoma of the anal mucosa.

The most important physical findings were those in the perianal region where the skin was superficially ulcerated. The mucocutaneous junction was irregular and nodular throughout its circumference. The anal canal was lined by redundant folds of skin and mucosa. Sigmoidoscopic and digital examination of the rectal ampulla was negative.

An abdominoperineal resection of the sigmoid colon, rectum, and anus, including a wide margin of perianal skin, was done Jan. 8, 1958. At the time of abdominal exploration no significant adenopathy was noted along the course of the aorta. However, a single mass measuring 3 by 3 cm. was found on the leading edge of the right lobe of the liver, immediately superior to the fundus of the gall bladder. The mass was not umbilicated. It was located so far upward in the abdomen that direct visualization of the lesion was impossible. After palpation, however, the mass was thought to be a metastatic deposit.

On gross examination the specimen showed no intraluminal masses within the anus or rectum except for thickened elongate folds in the anal canal. Subsequent microscopic study showed that the adenocarcinoma had apparently been completely excised by the local procedure performed before entry into the hospital. The lesion in the perianal skin was caused entirely by intraepithelial spread of the mucoid adenocarcinoma (Figs. 1 and 2).

CASE 2.—A 76-year-old white man was first seen at the San Francisco General Hospital in October, 1956. Induration of the skin of the left upper anterior thigh, scrotum, and lower abdomen and a plaquelike induration of the left inguinal region were present (Fig. 3).

Roentgenograms in the pelvis and lumbar spine showed an osteoblastic lesion in the fourth lumbar vertebra. After investigation the Tumor Board made a diagnosis of sweat-gland carcinoma arising from the skin of the left inguinal region, with metastases to inguinal and pelvic lymph nodes. It was mentioned at that time that metastatic carcinoma could not be definitely ruled out. The lymphedema was believed to be due to lymphatic obstruction from lymph-node metastases. Irradiation therapy to the iliac and inguinal nodes on the left side was given in an effort to relieve the lymphatic obstruction. A biopsy of the lesion on the skin and of an inguinal lymph node before therapy was begun indicated the presence of adenocarcinoma, the origins of which could not be definitely determined from the microscopic appearance alone.

Three months later, in January, 1957, the patient was readmitted to the hospital for treatment of moderately severe congestive heart failure. By this time he had developed supraclavicular lymphadenopathy which showed the presence of adenocarcinoma. No further bony metastases were noted. The lung fields were free from metastatic disease.

Acid-phosphatase determinations on previous admissions had been 40 or above. A needle biopsy of the prostate gland failed to reveal malignant disease. The prostate, however, was extremely firm in all areas. The entire prostatic area was infiltrated by March, 1957, as was most of the left side of the pelvis.

A clinical diagnosis was made of carcinoma of the prostate gland with metastases to the lumbar spine, pelvis, sacrum, regional, periaortic and clavicular nodes, and the skin of the inguinal region. The patient was readmitted to the hospital in March, 1957, and was treated by orchiectomy, stilbesterol therapy, and radiation to the lower pelvis in an effort to relieve the lymphatic obstruction.

The patient's condition became worse and he died on May 27, 1957. Autopsy showed adenocarcinoma of the prostate gland with direct extension into the pelvic soft tissue and invasion of the left ureter, with mild hydronephrosis. Metastases were found in the skin and subcutaneous tissue of the anterior abdominal wall, legs, inguinal, mediastinal and supraclavicular nodes and bone marrow (Fig. 4).

SUMMARY

Two cases have been presented which lend support to the thesis that Paget's disease represents secondary malignant intracutaneous spread from underlying

Fig. 1.

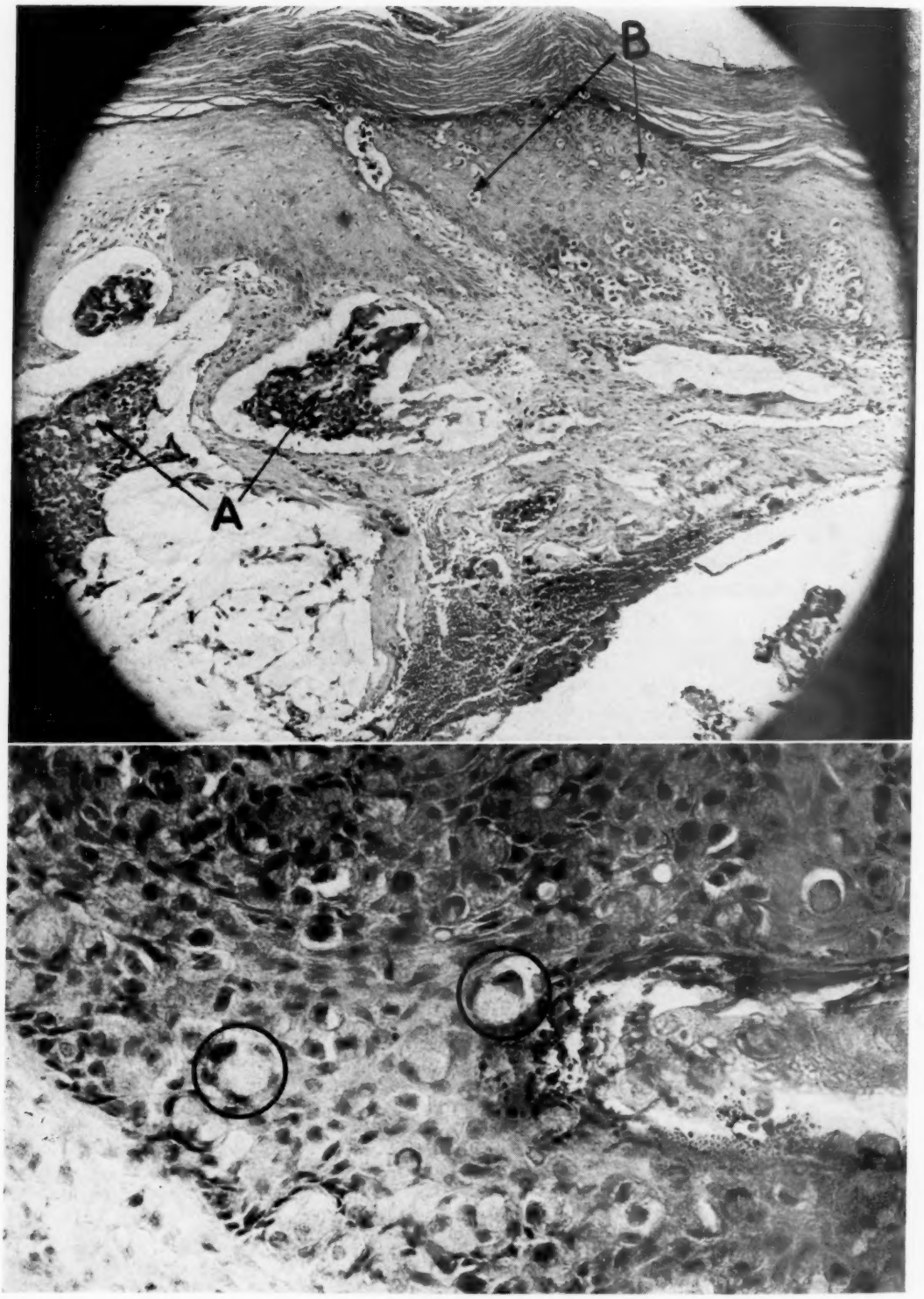

Fig. 2.

Fig. 1.—Case 1. Photomicrograph (×100) showing mucoid adenocarcinoma invading the perianal subcutaneous tissue (*A*). Paget's cells are present in abundance in the skin (*B*).

Fig. 2.—Case 1. Photomicrograph of skin (×300) showing Paget's cells. Mucicarmine stains demonstrated that these cells contained mucin identical in staining characteristics with the underlying carcinoma.

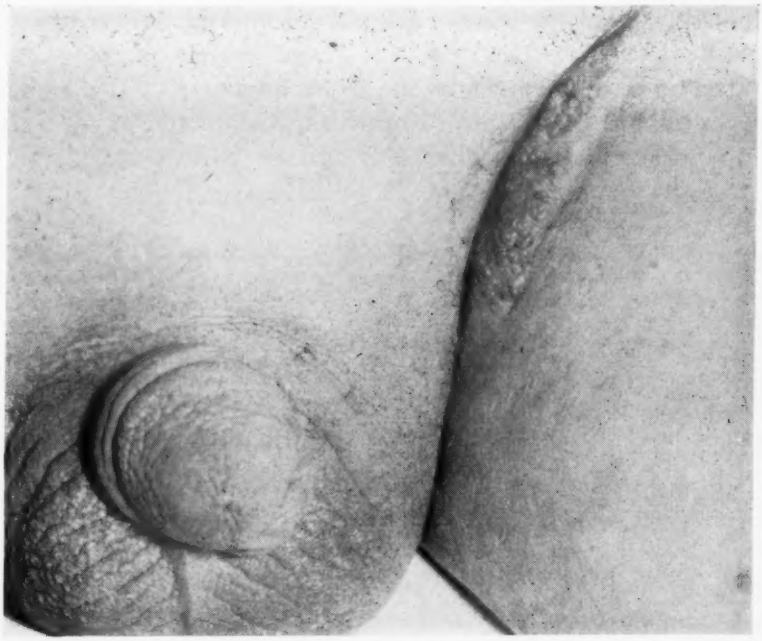

Fig. 3.—Case 2. The scaly, finely lobulated lesion in the left groin is accompanied by lymphedema of the upper thigh and pubic region.

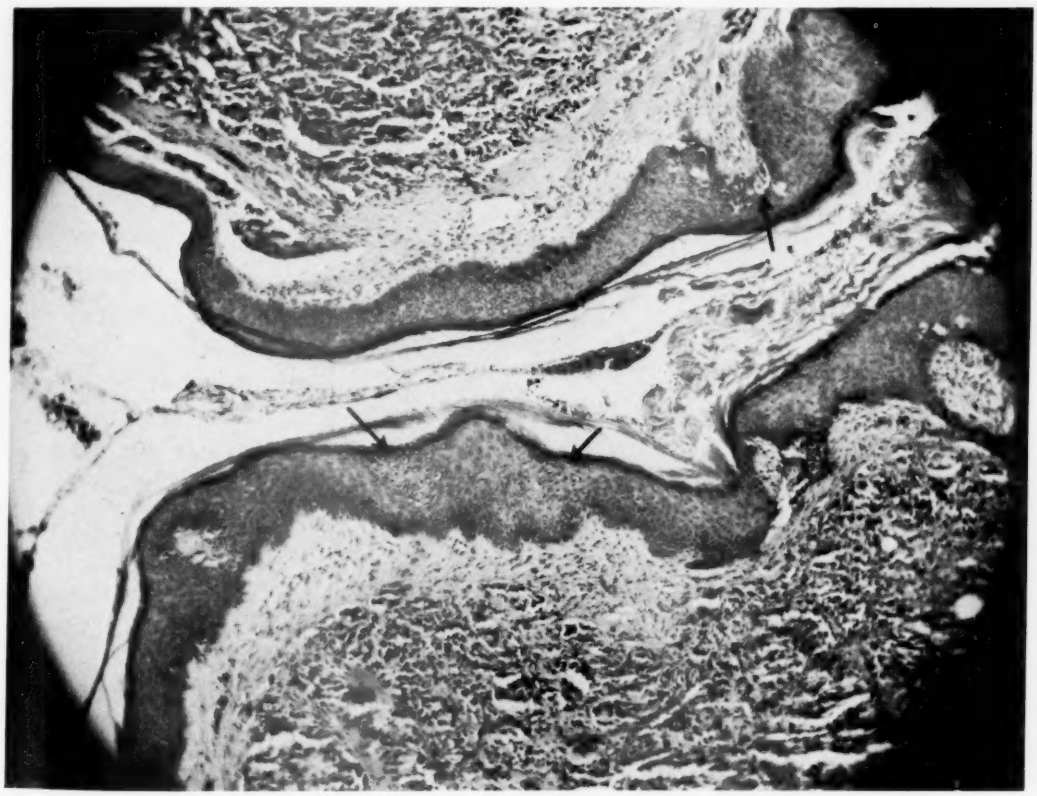

Fig. 4.—Case 2. Photomicrograph (×100) of skin, subcutaneous tissue, and lymph node from the left inguinal region. Prostatic carcinoma metastatic from the pelvis to the node was also present in the skin (indicated by arrows), appearing as Paget's cells.

primary carcinoma. The primary tumors were mucoid adenocarcinoma of the anal canal and carcinoma of the prostate. Special stains showed mucoid material in the Paget's cells similar to that which occurred in the underlying carcinoma. It is probable that Paget's disease represents merely an unusual mode of spread to the skin along established lymphatic pathways.

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REPAIR OF THE INJURED URETER

A New Technique for End-to-End Anastomosis

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PRACTICALLY all injuries of the ureter result from surgery. Not more than half a dozen instances of injury to the ureter from external trauma were observed in 47 months of general hospital duty during World War II.* However, almost every gynecologist or abdominal surgeon at some time is confronted with the problem of a severed ureter. The situation having arisen is urgent and demanding. Preservation of the kidney is a serious consideration and indeed the life of the patient may be in danger. Several questions immediately arise: (1) Shall an attempt be made to anastomose the cut ends? (2) What method of anastomosis gives the best long-term results? (3) Is it safe to ligate the cut ureter and return it to the abdomen? (4) What measures can be taken to prevent this accident?

Shall an attempt be made to anastomose the cut ends? Yes, the ureter should be anastomosed, and if it is done properly a good result can be anticipated. A well-functioning unobstructed ureter is indispensable in preserving renal function. It is not a static drainage tube but a dynamic tubular viscus whose peristalsis is synchronized with that of the renal calyces and pelvis.

Before closing the abdomen after a difficult operation, a careful inspection of tissues is warranted in an effort to determine if injury has occurred. In the normal abdomen the ureters can be seen through the posterior parietal peritoneum on either side as they course over the brim of the true pelvis and traverse the point where the common iliac vessels divide, following the internal iliac artery for a distance as they pass downward toward the bladder. Most injuries occur in this area.

Upon discovery that the ureter is severed, it is usually the proximal end that is found. The distal segment may contract into the obscure and perhaps anatomically disturbed reaches of the pelvis. If the distal segment cannot be located, a cystoscope can be introduced into the bladder, or the bladder can be opened, allowing a catheter to be passed up the ureter. The catheter can be palpated or seen to emerge from the distal segment.

This study was supported in part by U.S. Public Health Service Grant H-2908.
Received for publication Aug. 25, 1958.

*Personal experience (F. C. H.): There were only 27 wounds of the ureter in 3,154 abdominal injuries (0.86 per cent) recorded in World War II. Surgery in World War II, Volume II, Office of the Surgeon General, Department of the Army, Washington, D. C., 1955.

What methods of anastomosis give the best long-term results? In the past, results following anastomosis of the ureter have been poor, so poor, in fact, that as recently as 1954 Moore[1] stated that it was probably not worth while since "in the majority of cases stricture at the site of anastomosis is almost inevitable." We[2] have developed a technique that has given good results in the experimental animal and in the human subject. This technique is similar to that proposed by Soresi[3] for intestinal anastomosis and has as its objects the widening of the lumen at the point of anastomosis and the production of an oblique suture line.

Both ends of the ureter are mobilized for only a short distance; about 1.5 cm. on either side is sufficient. It is probably redundant to caution against trauma. The ends of the ureter are not clamped or tied. A small amount of urine may be discharged from the proximal end, but if the kidney is normal and the urine is uninfected (as determined by urinanalysis preoperatively) there is little danger from infection. The ureter should not be mobilized widely for the following reasons: Its main blood supply comes from either end, above from the renal vessels and below from the vesical arteries (internal iliac). Additional small arteries supply it throughout its course. A rich plexus of vessels are present in the outer layer of the ureter. Unnecessary handling damages the vascular plexus. Extensive mobilization of the ureter from its bed may also result in stretching, rotating, or otherwise altering its course so that obstructive curves or angulations result. It is a little more difficult for the surgeon to work in the depths of the wound, but better results are obtained than from pulling the ureter up into the field.

The severed ends of the ureter are incised in the longitudinal direction for a distance of 1 cm. on the dorsal aspect of the distal segment and a similar distance on the ventral aspect of the proximal segment. These incisions produce a broad spatulated effect at the ends of the ureteral segments (Fig. 1).

A stitch of 5-0 atraumatic catgut is then placed in the tip of the spatulated end of the distal ureter and sutured to the apex of the V of the proximal ureteral segment. In the proximal ureter the reverse is done, joining the end of the distal ureter. The first two sutures are tied and cut long to be used as guides. Several interrupted or everting mattress sutures are then placed on either side, approximating mucosa to mucosa. No attempt is made to obtain a water-tight closure as a suture line will not hold if there is obstruction below the line of anastomosis. One row of sutures is sufficient. Excessive suturing results in fibrosis and stricture. Nonabsorbable suture material should never be used as it is difficult to avoid penetrating the wall of the ureter and urinary salts will precipitate on a silk or cotton suture in contact with urine and a calculus will be formed.

This method has the advantages that (1) the circumference of the ureter at the site of anastomosis is increased and (2) the suture line follows an oblique oval course rather than a transverse round direction. Some contracture at the suture line probably happens, but a moderate contracture of the oval oblique suture line will not produce obstruction.

Dividing the ureter in any segment of its course results in a profound but temporary disturbance in its physiology.[4] Peristalsis which normally follows and is synchronous with contraction of the renal pelvis proceeds down to the point of division where the wave stops. The segment below the suture line assumes a reduced asynchronous peristaltic pattern (Fig. 2). As a result, urine propelled down the proximal segment may encounter the lower segment in a contracted phase, which results in a building up of pressure and

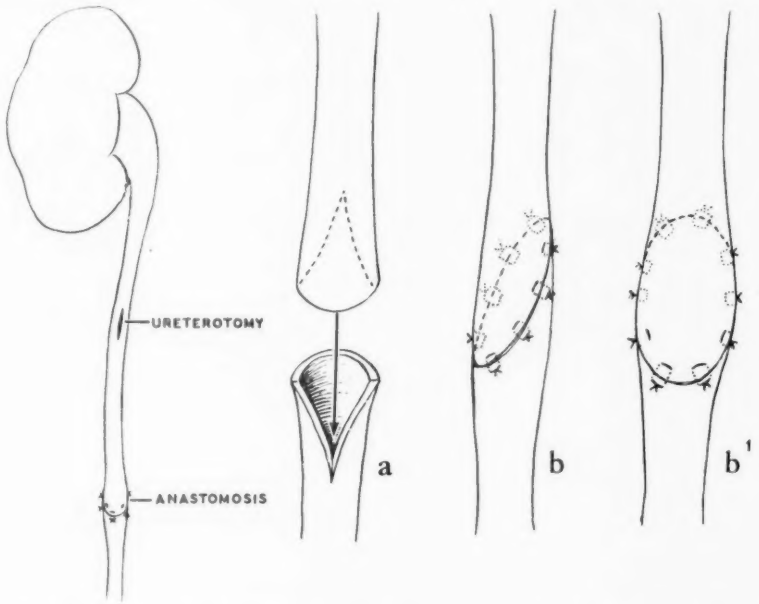


Fig. 1.—Technique of oblique end-to-end anastomosis of the ureter. The spatulated ends are joined with 5-0 chromic, everting sutures. A linear incision is made in the ureter well above the site of anastomosis for drainage and release of pressure from the suture line.

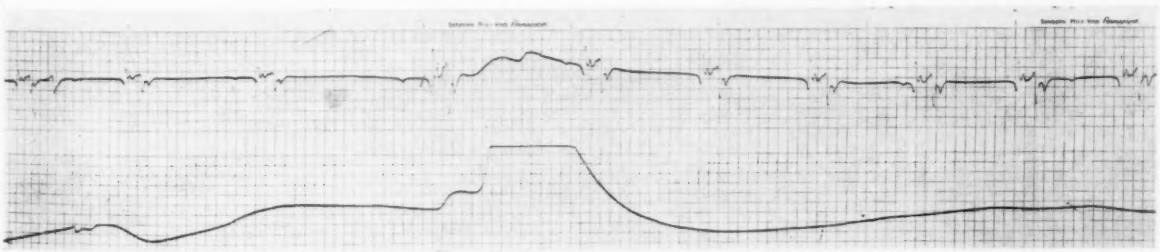
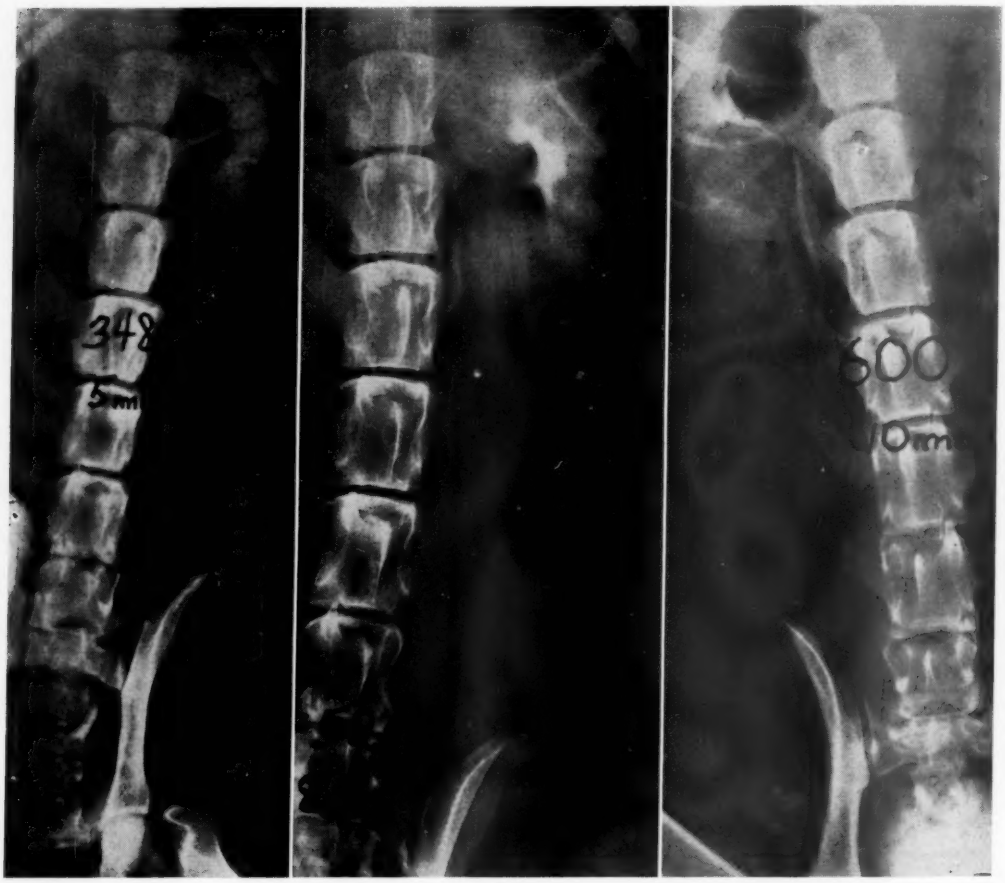


Fig. 2.—Simultaneous recordings of action potentials from the proximal and distal portions of a severed ureter. *A*, Normal peristaltic curve found above the transverse section. *B*, Curve recorded distal to transverse section. Regular synchronous contractions are absent.

dilatation in the upper segment. One of the possible causes for poor results from anastomosis in the past has been a failure to provide for relief of pressure on the suture line. Escape of urine and relief of pressure is provided by making a linear incision in the ureteral wall above the site of anastomosis.

A ureteral catheter may be placed in the lumen of the ureter during the time required for anastomosis as an aid in placing the sutures, but this is removed as the last suture is tied. It is not necessary to have any splint or catheter during the healing period. The T tube has been advocated by some

surgeons. Objections to the use of the T tube are that it may become obstructed by deposits of urinary salts. A foreign-body reaction (thickening and fibrosis) of the ureter may result, and finally a tube of this type exposes the ureteral epithelium to the external environment resulting in infection with drug-resistant organisms.



A. *B.* *C.*

Fig. 3.—Excretory urograms demonstrating results of end-to-end anastomosis of the ureter in 6 dogs. No. 349 was done on both sides. *A*, 5 months postoperatively; *B*, 8 months; *C*, 10 months; *D*, 11 months; *E*, 1 year; and *F*, right 1½ years and left 1 year.

A rubber tissue drain is passed retroperitoneally down to the site of the linear incision and another to the site of the anastomosis. They are allowed to remain for a period of not less than 9 days since some leakage is inevitable and, if free drainage is not provided, extravasation of urine with severe periureteral fibrosis results. These patients are all required to stand out of bed 8 hours after operation and daily thereafter if their condition permits. It requires 10 to 14 days for the ureter to heal solidly.

If it is discovered that the ureter has been severely crushed or otherwise traumatized so that the vascular network is damaged for a short distance (2 to 3 cm.), this area should be resected since the possibility of stricture is considerable. The ureter should be mobilized enough to bring the ends to an

overlapping position, as previously described, and anastomosis done. There is no known method for bridging large complete defects in the ureter without a high incidence of stricture formation. Our attempts to bridge defects of 3 cm. or more in length in the experimental animal (6 dogs) by use of bladder mucosa failed. Other methods of repair are indicated here, if near the bladder a reimplantation may be done or larger defects may require complete or partial substitution with a segment of ileum.

D. *E.* *F.*

Fig. 3 Cont'd.—*For legend see opposite page.*

Is it safe to ligate the cut ureter and replace it in the abdomen? Instances are recorded where the ureter has been ligated and the kidney died silently and without any serious upset aside from a moderate flank pain that could be overlooked during convalescence. On this basis there are occasional discussions and revival of the idea that it is a safe procedure. This has not been our experience. It was done in 3 patients in whom no satisfactory disposition of the ureter could be made without further extensive surgery that could not be tolerated by the patient. In each instance further surgery had to be carried out. Either the suture sloughed off and a urinary fistula was produced or pain and infection required interference. Unless the urinary tract has been surveyed, which it should be in most instances, one is never

quite sure that the ureter to a congenital solitary kidney (occurrence 1 in 1,000) is not being ligated. Palpation of a kidney on the contralateral side is reassuring, but there remains the danger of function being reduced until it is inadequate to support life. Generally speaking, it is a risky, unreliable procedure.

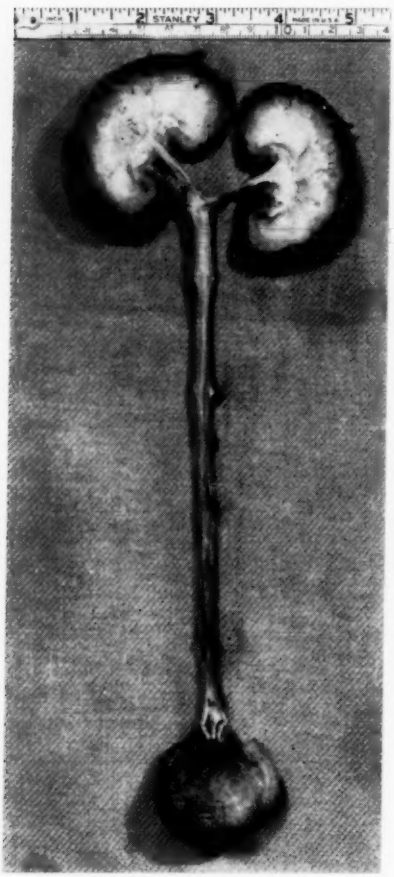


Fig. 4.

Fig. 5.

Fig. 4.—Specimen of kidney and ureter removed from Dog 349 1½ years after anastomosis. Kidney bisected, repair excellent. The site of anastomosis can hardly be detected.

Fig. 5.—Case 1. Pyeloureterogram done 20 months postoperatively. This patient is now 3 years without symptoms of obstruction.

What measures can be taken to prevent this accident? A urologic survey with visualization of the upper urinary tract will give useful information as to the status of kidney function before an extensive abdominal operation is contemplated. It is almost routine for the gynecologist to request this type of information before abdominal surgery, particularly the radical operations for cancer. A urologic workup is also done on all patients with any type of abdominal tumor. There are sound reasons for this. (1) The urinary tract is a frequent site of origin for tumor. (2) When the tumor does not arise from the urinary tract, pyelograms may be of considerable value in localizing it. If displacement of the ureter or kidney is observed, the tumor is presumed to be in the retroperitoneal space.

A catheter in each ureter during a difficult surgical procedure can be of great comfort to the surgeon when one anticipates that the anatomy will be disturbed (radical gynecologic operations and the more difficult abdominoperineal operations). The catheters are inserted immediately before operation. Pyelograms are made since they add nothing to the procedure and serve

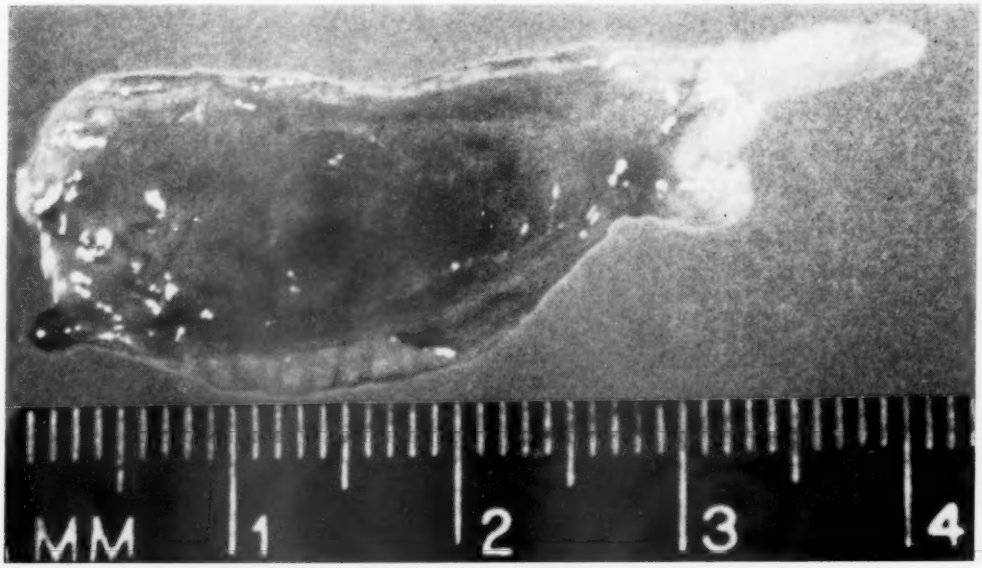


Fig. 6—Case 2. Diverticulum of left ureter removed with 4 cm. of ureter.

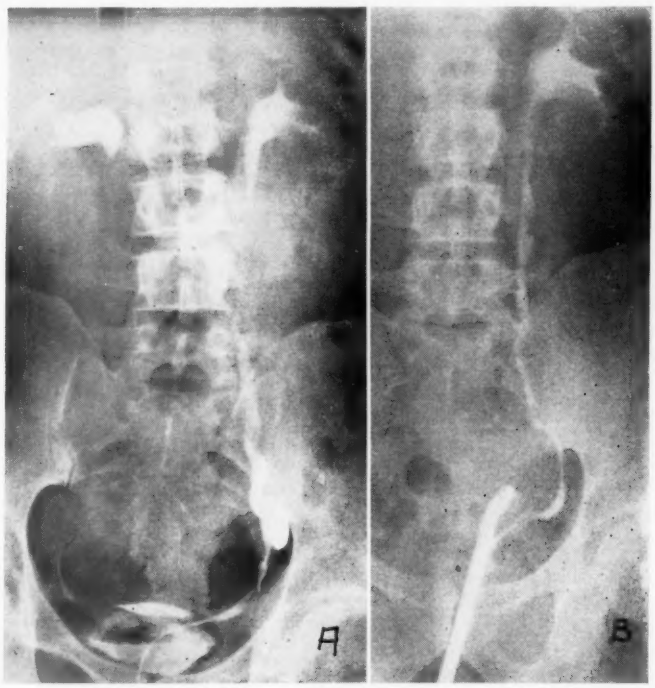


Fig. 7.—Case 2. Diverticulum of the left lower ureter. *A*, Preoperative film. *B*, Film taken 9 weeks after operation. Patient is free of symptoms on 18 months' follow-up.

to establish the status of the kidneys. A Foley catheter is passed into the bladder to provide continuous drainage and also to serve as an anchor for the ureteral catheters which are tied to it. The ureteral catheters are removed immediately after operation.

RESULTS

Experimental.—Six dogs, one having bilateral operations, survived the postoperative period (7 operations on 6 dogs). The animals were observed for varying periods to determine the effect of the operation on the function of the involved kidney. Fig. 3 is a composite plate of the excretory urograms taken of each of the animals. It will be noted that normal renal function and morphology was noted as long as 1½ years after the operation.

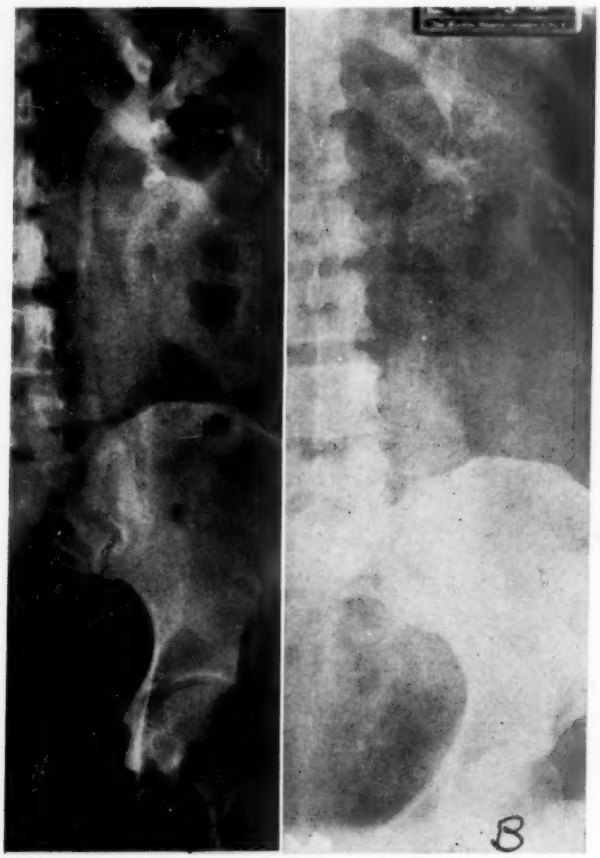


Fig. 8.—Case 3. End-to-end repair of left severed ureter during course of hysterectomy. *A*, Excretory urogram taken 12 days following anastomosis; note slight temporary dilatation of the upper left ureter and calyces. *B*, Urogram taken 35 days after operation with healing complete and normal pyeloureterogram. Patient is free of symptoms on 13 months' follow-up.

After the urograms were obtained the animals were sacrificed to study the microscopic appearance of the healed anastomoses and the involved kidneys. The sections were stained differentially for scar tissue by the Gomori stain. In all instances the site of operation in the ureter was revealed as a

line scar surrounded by normal muscle. Sections taken from each kidney drained by the anastomosed ureter showed no deviations from normal. Fig. 4 is a photograph of a gross specimen removed 1½ years after anastomosis from Dog 349. One can hardly identify the site of anastomosis and there is no ureterectasis or calyectasis above this point.

Clinical Experience.—Fortunately the need for this operation is not frequent. Four patients have been subjected to this procedure as follows:

CASE 1.—M. S. was a 44-year-old white man. His right ureter was severed while undergoing ligation of the inferior vena cava in April, 1955, on the General Surgical Service, University Division, Kings County Hospital. The technique of oblique anastomosis of the spatulated ends was carried out, but no diversion of the urine was provided for by a linear incision above the site of anastomosis since this refinement of the technique had not yet been developed. Some dilatation of the proximal segment was present for over 6 weeks. However, he made a good recovery and he is living and well 3 years later without obstructive symptoms. No dilatation or instrumentation has been required. Fig. 5 is a pyeloureterogram taken on Dec. 11, 1956, 20 months postoperative. The site of anastomosis can be seen as a bayonet type of deformity, but there is no evidence of obstruction.

Fig. 9.—Case 4. Excretory urogram. Right ureter severed and anastomosed directly over a catheter during radical hysterectomy. *A*, Excretory urogram taken 48 hours post-hysterectomy and ureteral repair; patient had severe pyelonephritis. *B*, Retrograde ureteropyelogram 6 weeks after operation; patient is free of infection and symptoms.

CASE 2.—There had been a history of three episodes of pyuria accompanied by chills and fever in this 32-year-old white man. Retrograde pyelography demonstrated a diverticulum in the lower segment of the left ureter. Complete resection of this area including 4 cm. of the ureter (Fig. 6) was done, followed by end-to-end anastomosis and diversion ureterotomy (S. R. W.) on Aug. 8, 1957. Follow-up pyelogram on Oct. 14, 1957 (Fig. 7) demonstrates good repair and no evidence of obstruction. The patient is free of symptoms and urinary infection has not recurred.

CASE 3.—M. G. was a 41-year-old Negro woman. Hysterectomy was done for fibromyomata uteri on May 31, 1957. While freeing the left infundibulopelvic ligament, the left ureter was clamped and cut. Urologic consultation was requested. End-to-end anastomosis and diversion ureterotomy (F. C. H.) was done. The patient was discharged from the hospital on the fourteenth postoperative day, July 16, 1957. It is remarkable that there was very little urinary drainage for the first 4 days postoperatively and none thereafter (Fig. 8).

CASE 4.—E. A., a 26-year-old white woman, was an example of a poor immediate result following another technique later corrected. She had a radical hysterectomy on Aug. 16, 1957, for carcinoma of the uterus. The right lower ureter was inadvertently severed. The gynecologist opened the bladder, passed a ureteral catheter through both segments, and anastomosed the severed ends. The splinting catheter was allowed to remain indwelling and no ureterotomy vent was provided. On the first postoperative day the patient had a high fever and pain in the flank and back. A palpable fluctuant mass was noted in the right flank. An excretory urogram showed pyelectasis and incomplete filling of the right kidney (Fig. 9, *A*).

On August 19, a second operation by W. P. (Instructor, University Division) was done. The ureter was identified and found surrounded with purulent urine. A diverting ureterotomy was done after the splinting catheter was removed. The anastomosis was examined and found to be satisfactory, it was not disturbed (Fig. 9, *B*). The patient made a good recovery and has been free of symptoms since the second operation.

SUMMARY

A new technique for anastomosis of the severed ureter is described. This technique has given satisfactory long-term results in the experimental animal and in 4 patients whose histories are given in summary.

Crushing injuries of the ureter during surgical procedures that may lead to urinary fistula formation or stricture should be treated by resection and anastomosis. Ligation of the proximal severed end of a ureter to induce asymptomatic atrophy of the companion kidney usually leads to difficulties necessitating secondary operation.

Injuries to the ureter during surgery may be prevented by preoperative roentgenographic localization of the position of the ureter and by the preoperative insertion of ureteral catheters where difficult pelvic dissections are anticipated.

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PARTIAL RESECTION OF THE RIGHT KIDNEY AND RADICAL REMOVAL OF THE LEFT KIDNEY IN A PATIENT WITH BILATERAL HYPERNEPHROMA

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AND

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COMPLETE extirpation of the primary tumor has not been attained in any of the reported cases of bilateral hypernephroma.†[1-6, 10-14, 16-32, 34, 35]

Colston[9] and Watts[33] each performed partial nephrectomy for tumor occurring in a solitary kidney. Close, Peterson, and Johnson[8] reported the 3 year survival of a case of bilateral embryoma of the kidney treated by partial nephrectomy on one side and complete nephrectomy of the opposite side followed by irradiation therapy. However, not all of the known tumor was removed.

In this paper we present a case of bilateral hypernephroma, with a history of kidney tumor in one parent, treated by partial excision of the right kidney and radical left nephrectomy followed over 5 years without evidence of recurrence.

Familial malignant hypernephroma in conjunction with hereditary cysts is reported by Clemmesen.[7] Greene and Rosenthal[15] report 2 independent hypernephromas in the same kidney in an individual with Lindau's disease. Lewis and Kimbrough[23] treated a case of bilateral hypernephroma associated with polycystic disease in 1952.

CASE REPORT

F. H., a 37-year-old white married male mechanic was referred to the Minneapolis Veterans Administration Hospital by Dr. Brian McGroarity of St. Paul on April 7, 1952. The patient complained of gross total hematuria on two occasions during the 2 weeks immediately preceding admission. On one occasion the hematuria was accompanied by pain in the left flank. While he was in the military service in 1942, the patient had an operation for left epididymitis. There were no other symptoms referable to the genitourinary organs. A year before the onset of the present illness he had been placed on a diet for peptic ulcer. There were no ulcer symptoms at the time of admission. He had lost 20 pounds in the preceding 3 years. The patient's father had a nephrectomy for "cancer of the kidney" in 1929 and died 2 years later at the age of 45, presumably with brain metastases. No

Received for publication Sept. 8, 1958.

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†The terms hypernephroma, renal cell carcinoma, and adenocarcinoma of the kidneys are considered synonymous in this paper. Hypernephroma was chosen for the title because of its long and common use.

postmortem examination was done. Specimens and records from the original operation are not available. The patient's mother and only sibling were living and well. Physical examination revealed a small white man in no acute distress who appeared to have lost weight recently. Eyes, ears, nose, and throat were essentially negative with no cervical lymphadenopathy. He had many teeth missing. The heart and lungs were normal. The lower pole of the left kidney was palpable and tender. There were no other abdominal masses. Both testes were small and soft. Tenderness was elicited on Murphy percussion bilaterally, but was more marked on the left. There were discrete firm axillary nodes bilaterally. Admission urinalysis: specific gravity, 1.016; albumin, faint trace; sugar, none; microscopic examination, 3-5 wbc/hpf. Hemoglobin, 14.2. White blood count, 9,500 with 66 per cent neutrophils, 28 per cent lymphocytes, 4 per cent monocytes, 1 per cent eosinophils, and 1 per cent basophils. Sedimentation rate was 1 mm. Urine culture grew *Pseudomonas aeruginosa*. Serology was negative. BUN was 12.8 mg. per cent.

Fig. 1.

Fig. 2.

Intravenous urography and bilateral retrograde pyelograms revealed definite distortion of the entire left calyceal system and minimal distortion of the upper minor calyces on the right side (Fig. 1). Aortography confirmed the suspicion of left renal neoplasm and suggested the presence of neoplasm at the lateral margin of the upper pole of the right kidney as well (Fig. 2).

Because of these findings, the right kidney was explored through the usual lumbar incision with excision of the twelfth rib on April 17, 1952. Numerous clear cysts were seen protruding from the cortex of the kidney, but apparently not within it. On the upper pole were two rather large cysts which were not filled with clear fluid, but appeared white to yellow in color. From an incision made into one of these cysts soft yellow tumor tissue protruded. The pathologist's report on frozen section was hypernephroma. A right partial nephrectomy was done after a tourniquet was placed about the renal pedicle. Hemostasis was obtained by ligating the visible individual arteries then placing mattress sutures below

Fig. 3.

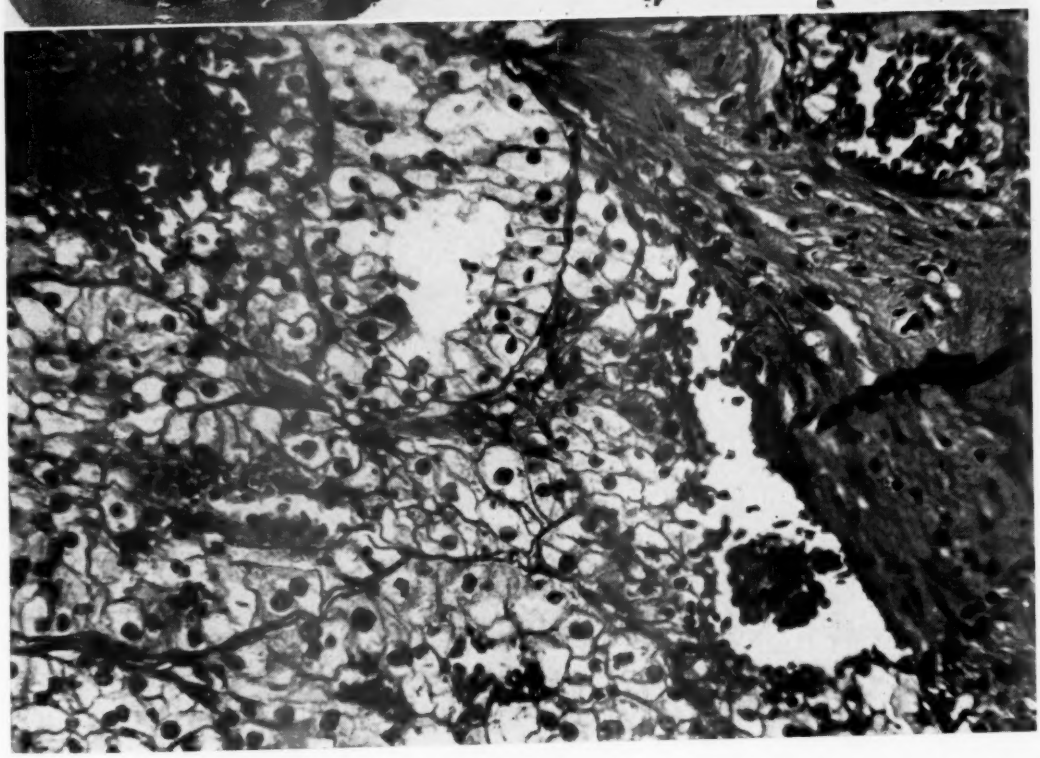

Fig. 4.

Fig. 5.

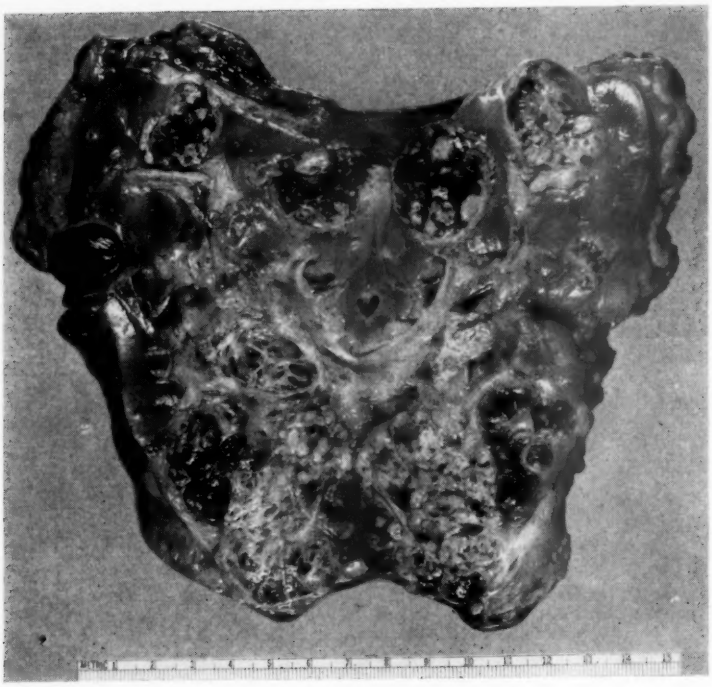

Fig. 6.

Fig. 7.

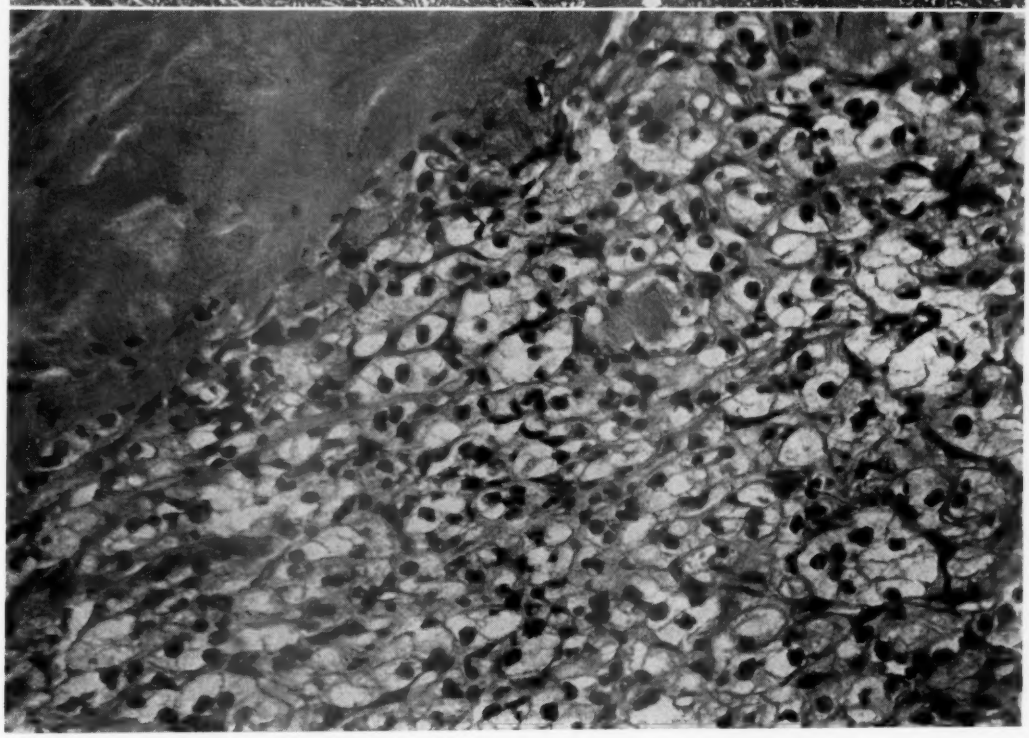

Fig. 8.

the line of excision and tying them over fat. A piece of perirenal fat was then placed in the defect and the cortex was brought together over this with sutures through the parenchyma. Two Penrose drains were left down to the kidney and the wound was closed in the usual fashion.

Pathology Report I (Figs. 3 and 4).—

Gross appearance: The specimen consisted of a 6 by 4 by 2.5 cm. wedge-shaped portion of kidney most of which consisted of tumor with only a very narrow rim of kidney surrounding it. The tumor itself on cut section was partially cystic, but consisted of large red hemorrhagic areas interspaced with white and brilliant yellow soft areas. It was partially, but not completely, encapsulated.

Microscopic examination: The tumor itself was made up of large clear cells which were closely packed against each other without any significant stroma between them. Considerable hemorrhage had occurred in and through the tumor. Examination of the kidney itself revealed only compression changes as a result of the tumor.

Fig. 9.

Diagnosis: Adenocarcinoma of the right kidney was the diagnosis.

Convalescence was comparatively uneventful. On May 5, 1952, cystoscopy was done, a No. 10 Braasch bulb passed up the right ureter and differential P.S.P. test done followed by a pyelogram. Eight per cent of the dye was excreted by the right kidney in the first 15 minutes following injection. Intravenous urogram done on May 8, 1952 (Fig 5) showed prompt function on the right with an apparently normal collecting system. The left kidney was unchanged.

Having determined by P.S.P. test and excretory urography that the function in the remaining, tumor-free portion of the right kidney appeared adequate to sustain life, left nephrectomy was done on May 9, 1952, through a Nagamatsu incision. The adrenal gland was separated from the upper pole and the renal pedicle ligated. After ligating the ureter,

the kidney was removed along with the surrounding fascia and fat. Two large Penrose drains were left in the renal fossa. A wound infection developed on the twelfth postoperative day, but healed readily after drainage. The remainder of the postoperative course was uneventful.

Pathology Report II (Figs. 6, 7, and 8).—

Gross appearance: The specimen submitted consisted of an entire kidney measuring 16 by 7 by 6.5 cm. The kidney was opened sagitally and there were many discolored yellow, red, and black areas present which were nodular in shape and consistency. The nodules measured 3 cm. in diameter and were found at both inferior and superior poles. The kidney capsule was thickened and contained firm areas suggesting tumor invasion. The average thickness of the cortex was 6 mm.

Microscopic examination: The nodules seen were grossly made up of masses of cells which had an extremely clear cytoplasm. This was a classical picture of hypernephroma. In one section it was noted that there was tumor in what may be a blood vessel and apparently the tumor cells were growing along the wall. The renal tissue had been markedly compressed by tumor nodules. In areas where kidney parenchyma was unaffected, the glomeruli appeared normal.

Diagnosis: Hypernephroma was the conclusion.

The patient has been followed in the clinic with periodic urograms, chest films, and sedimentation rates. He has been essentially well in the interim. No evidence of metastases exists at present. Laboratory studies done Nov. 18, 1957, were as follows: white blood count, 8,150, with a normal differential; hemoglobin, 16.2; sedimentation rate, 2 mm. Urinalysis: specific gravity 1.017, 0 albumin, 0 sugar, occasional wbc and rbc/hpf. BUN was 14. Chest x-ray revealed no evidence of active disease process. For sample films from the last urogram see Fig. 9.

DISCUSSION

We believe this case represents the first in which the definitive diagnosis of bilateral hypernephroma has been made prior to exploration or autopsy. We feel this would have been impossible without the aid of aortography. Whether or not the tumor in the right kidney is independent of the lesions in the left kidney remains unresolved, but the presence of dual apparently separate lesions in the left kidney suggests that the right kidney tumor is also independent in origin.

Since the left kidney appeared beyond salvage, the plan of treatment was that if a portion of the right kidney, adequate to sustain life, could be saved there was some hope for the patient. Therefore, the right kidney was explored first and the portion bearing tumor was resected. Intravenous urography and differential P. S. P. tests revealed adequate function remained. Radical left nephrectomy was then carried out.

The patient is alive, well, and has been working regularly for over 5 years since his surgery.

We are indebted to Dr. Donald Gleason, Instructor in Pathology, University of Minnesota, and the Pathology Department of the Minneapolis Veterans Administration Hospital for the pathologic diagnosis.

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PROBLEMS IN THE DIAGNOSIS AND TREATMENT OF ECTOPIC URETERAL ORIFICES

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THE variations from normal with which nature has plagued the human body have presented many interesting and difficult problems of diagnosis and treatment in all fields of medicine. It is an accepted pathologic axiom that anomalous organs are more subject to disease than their normal counterparts. While, within apparently normal individuals, many of these anomalies may remain symptomless and unrecognized, it can be anticipated that these anomalies will make themselves manifest in symptomatology and signs in one of two ways: either through their anomalous structure, or by the effects of disease resulting within these anomalous organs.

The increasing awareness of the presence of ectopic ureteral orifices has resulted through the years in an increased instance of diagnosis. Burford, Glenn, and Burford[1] were able to review the literature and report 425 cases of ureteral ectopia, including 2 cases of their own. The incidence has been quoted approximately 1 to 1,600; appearing about five times more frequently in the female than in the male. With the increasing number of cases reported, there seems to be little predilection for either side. Except in rare instances, this anomaly occurs almost entirely with reduplication of the kidney and ureters. The embryology has been adequately covered in many articles. It results from (1) the failure of the terminal position of the lower ureter, draining the upper renal pelvis, to migrate cranially as it is absorbed into the bladder analogue; or (2) the persistent relationship of the ureter with the wolffian or müllerian ducts.

While urinary incontinence has been stressed as the presenting symptom or complaint in the presence of this condition in the female, it is apparent from reviewing the literature and our experience that this is not true. Of 5 cases, in which we have established the diagnosis, urinary incontinence was present in only one individual. In evaluating individuals, especially females, with urologic complaints and recurrent pyuria, it is essential that the presence of an ectopic ureteral orifice be considered. Five cases will be presented to substantiate this statement.

CASE REPORTS

CASE 1.—J. V. (G. H. No. 11418), a 33-year-old woman, was referred for urologic evaluation because of a cyst in the vagina. On physical examination this was quite evident, lying below and to the right of the urethra near the neck of the bladder. It was about 5 cm. in diameter, soft, fluctuant, and nontender. The patient's urinary history

Received for publication Oct. 24, 1958.

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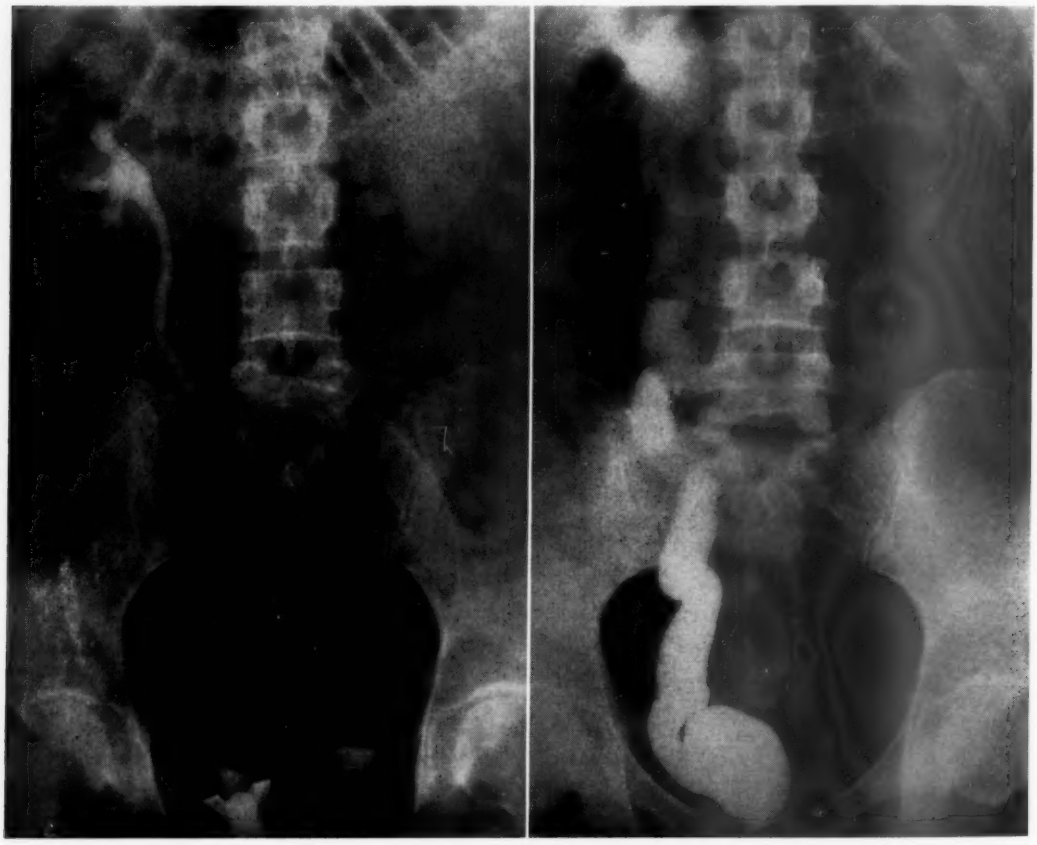
was essentially negative except for an attack of cystitis at the age of 17. She had suffered with a chronic backache since her early teens which had defied orthopedic and neurological evaluation. She received physiotherapy weekly with some relief. Since her early teens she had noted a persistent vaginal discharge of minimal to moderate degree which she treated with douching. There was no history of febrile episodes. An intravenous pyelogram was essentially within normal limits except that the right kidney seemed to be pushed slightly laterally and the presence of additional renal tissue without calyceal drainage seemed to be present in the upper pole (Fig. 1, *A*). Cystoscopy and panendoscopy failed to reveal the presence of an ectopic ureteral orifice. A cystourethrogram was normal. Indigo carmine was administered intravenously without visualization of excretion except from the normal ureteral orifices. Vaginoscopy failed to reveal the presence of an opening in the vagina. With the speculum in the vagina, the cyst was punctured with



A. *B.*

Fig. 1.—A, An intravenous pyelogram showing lateral displacement of the functioning portion of the right kidney. *B*, Transurethral vaginal retrograde pyelogram showing large dilated ectopic hydroureter on the right.

a No. 20 needle and 50 c.c. of clear fluid, resembling urine, was removed. This was replaced with 50 c.c. of 15 per cent Diodrast and x-rays were taken. A large dilated lower ureter and ureteral segment were visualized with reflux of this dye up to a dilated cystic upper pole of the right kidney (Fig. 1, *B*). Heminephrectomy and total ureterectomy was performed in two stages. The postoperative course was benign. Since that time she has been free of backache and the vaginal discharge has been absent.

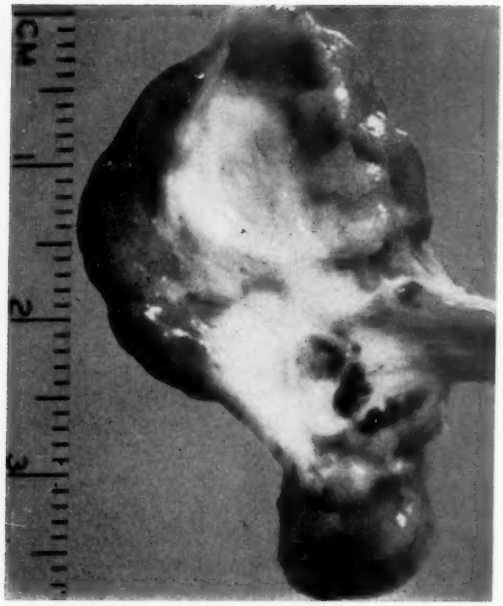
CASE 2.—G. M. (R. G. H. No. 10048), a 15-year-old girl, was referred for urologic evaluation because of persistent urinary wetting. The patient and her mother gave a history of extremely minimal but persistent urinary soiling, insufficient to soak through

the clothes but enough to spot and stain underclothes. There had been no history of febrile episodes and there was complete absence of urinary symptomatology. An intravenous pyelogram revealed reduplication of the kidney and ureter on the right side. On the left side the kidney seemed to be slightly moved laterally and there was a question of slight increase in the amount of renal tissue in the upper pole without calyceal drainage structures. Cystoscopy and urethroscopy revealed two ureteral orifices on the right side and one on the left. Panendoscopy did not reveal the presence of an ectopic orifice along the urethra or bladder. Vaginoscopy and vaginograms failed to reveal the presence of a ureteral orifice and there was no evidence of reflux into an ectopic ureteral opening. Indigo carmine was given on several occasions without visualization except through the known ureteral orifices. With the administration of intravenous fluids and injection of indigo carmine while observing the vagina, a small spot of dye was noted below the urethral meatus. A No. 5 catheter was passed with a forceps up this opening. A few drops of clear urine was obtained and retrograde pyelograms were made. A double kidney was also present on the left side with an ectopic ureteral orifice just below the external urethral meatus (Fig. 2, *A*). Heminephrectomy was carried out (Fig. 2, *B*). The postoperative course was benign. Urinary soiling has been absent since the day of operation.

Case 3.—S. S. (R. G. H. No. 9146), a 5-year-old girl, was referred for urologic evaluation because of recurrent severe febrile episodes accompanied by convulsions. There was no history of urinary symptomatology. A catheterized urine was negative on culture. An intravenous pyelogram revealed an essentially normal left kidney. On the right side there was poor excretion and poor function. The structures were not well delineated. A lower pole calyceal system and ureter were demonstrated with questionable reduplication. Cystoscopy and retrograde studies revealed a right ectopic ureteral orifice in the neck of bladder, the orifice serving a ureter draining the upper pole (Fig. 3, *A*). Exploration revealed a kidney which had been severely damaged by recurrent pyelonephritis. There was reduplication of the kidney and ureters. The kidney was small, atrophic, and severely scarred. While heminephrectomy had been anticipated, it was judged that complete nephrectomy would be the procedure of choice. Nephrectomy with partial ureterectomy was carried out (Fig. 3, *B*). Since that time the patient has been free of febrile episodes. No further convulsions have occurred and no urinary symptomatology has supervened.

Case 4.—S. G. (R. G. H. No. 10278), a 4-year-old girl, was referred for urologic evaluation because of recurrent pyuria and fever. She had been treated with antibiotics on each of four occasions in the preceding 8 months. The family sought further advice because of persistence of the recurrences. With each attack there was definite urinary symptomatology of frequency, burning, and dysuria which was absent in between attacks. There was no history of bed wetting or incontinence. An intravenous pyelogram revealed an essentially normal double kidney and double ureter on the right side. On the left side a normal kidney was visualized except that the kidney seemed to be pushed slightly laterally and there seemed to be additional renal tissue without calyceal drainage system. Cystoscopy and retrograde studies revealed two normal ureteral orifices on the right side. On the left side, an ectopic ureteral orifice was found at the neck of the bladder. Retrograde pyelography revealed a large, dilated, tortuous hydroureter and hydronephrosis from the upper pole of a double left kidney (Fig. 4, *A*). Heminephrectomy plus ureterectomy was carried out (Fig. 4, *B*). The postoperative course was benign. Following discharge from the hospital, recurrent pyuria and fever ensued. She was returned to the hospital where the remaining portion of the ureter down and into the bladder wall was resected. Again the postoperative course was benign but, following discharge from the hospital, she had two episodes of cystitis without fever but pyuria was present. Cystoscopic re-evaluation revealed that the intramural and intrabladder portion of this ectopic ureter was present and simulated a bladder diverticulum with a small orifice. It was felt that this resulted in (1) partial obstruction at the neck of the bladder, and (2) a persistent focus of residual urine. The bladder was explored suprapubically. The ectopic ureteral orifice was identified and the mucosa over the intrabladder portion of the structure was removed, bringing

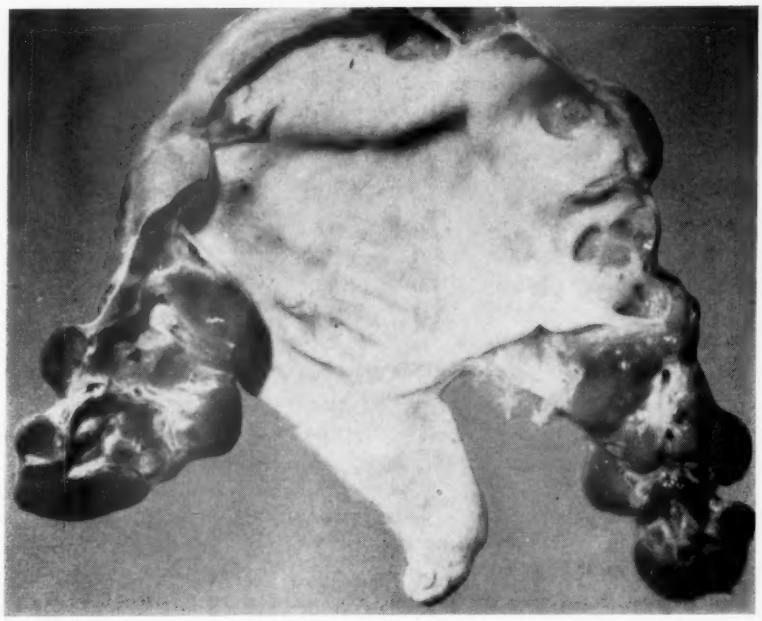
A.



B.

Fig. 2.—*A*, Transurethral vaginal retrograde pyelogram showing ectopic opening of ureter from the upper pole of a double kidney on the left. This opening was in the vagina below the urethral meatus. *B*, Gross specimen of heminephrectomy showing marked degeneration of the upper pole.

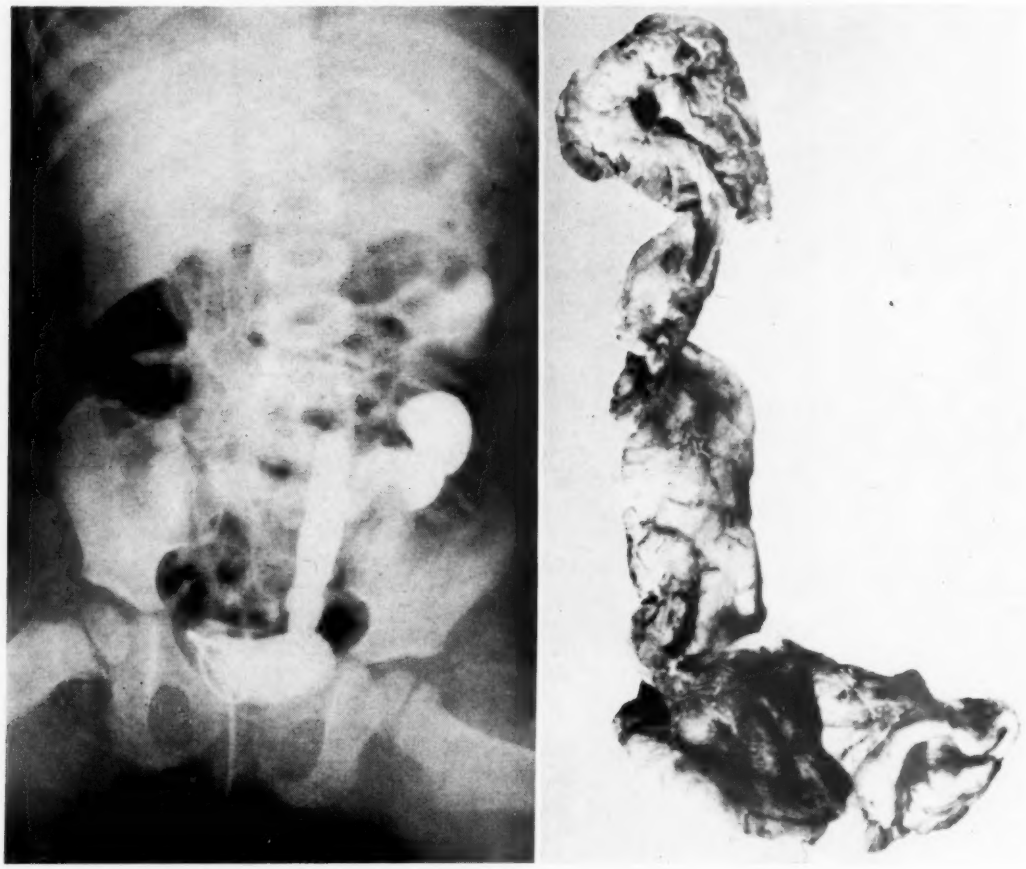
A.



B.

Fig. 3.—*A*, Retrograde pyelogram showing hydronephrosis and hydroureter with ectopic orifices in the bladder. *B*, Gross specimen showing marked hydronephrosis and renal atrophy.

this into continuity with the bladder. The edges were then sutured in continuity with the bladder mucosa and the bladder was closed. Foley catheter drainage was maintained. The postoperative course was benign. Since that time, over a period of 8 months, the patient has been asymptomatic and free of urinary difficulty.



A. *B.*

Fig. 4.—*A*, Retrograde pyelogram showing large dilated hydroureter and hydronephrosis with ectopic orifice in the neck of the bladder. *B*, Gross specimen showing the small degenerated renal segment and the large dilated ureter.

CASE 5.—J. M. (R. G. H. No. 11410), a 9-year-old girl, was referred for urologic evaluation because of recurrent attacks of pyelonephritis since the age of 2 years. No previous urologic evaluation had been carried out. An intravenous pyelogram revealed a single normal kidney on the right side. On the left side a relatively normal kidney was visualized except that it seemed to be pushed slightly laterally and there seemed to be some increase in renal mass not accounted for by a calyceal drainage system. Cystoscopy and retrograde studies revealed an ectopic ureteral orifice on the left in the neck of the bladder (Fig. 5). Exploration of the kidney was carried out with the intention of doing a heminephrectomy and partial ureterectomy. At that time an anomalous situation was discovered. A single artery and vein to the kidney entered in the region of the junction of the normal renal tissues of the lower pole with the small hydronephrotic upper pole. It was technically impossible to carry out a heminephrectomy. Therefore, as much ureter, as could be visualized through the incision, was excised up to the small upper renal pelvis which was transfixed and tied off. The patient's postoperative course was benign and she was discharged home without further difficulty.

DISCUSSION

In approaching any problem in pediatric urology the existence of anomalous structures of the genitourinary tract as a cause of symptomatology and pathology must be considered. In my experience it is unusual not to be able to establish the presence of some deviation from normal. While it is true that the majority of structural abnormalities are minimal in degree, that is,

Fig. 5.—Retrograde pyelogram showing double kidney on the left with the upper pole ureter draining into ectopic orifice at the neck of the bladder.

constricted meatus, vesical neck contracture, and so forth, they may still be the cause of serious urologic disease. The chronic recurrent pyelonephritis of the female, found in the presence of mild vesical neck obstruction, is an excellent example. Conversely, major urologic abnormalities, present in a much smaller percentage of the cases, may be found in the absence of extensive clinical disease. The first 2 cases exemplify this statement. Neither of these individuals had histories of recurrent pyuria or fever, or interference with general good health. The manifestations of their difficulties presented wholly because of structural abnormalities.

The last 3 cases were found in a search for the etiology of recurrent fever and pyelonephritis. The urine in all cases was negative for pyuria or infection at the time of the evaluation. A clean voided specimen with pyuria and a negative catheterized urine is a significant finding suggestive of an ectopic ureter.

In all 5 instances the diagnosis was considered and finally established prior to surgery. The most characteristic finding was the lateral displacement of the functioning portion of the double kidney, plus the enlargement of the involved kidney with an insufficient calyceal drainage system. Cystoscopically, in 4 of the 5 cases a ridgelike elevation of the mucosa was present in the trigonal area on the involved side. This is caused by the submucosal position of the ureter as it transcends the bladder toward its ectopic orifice.

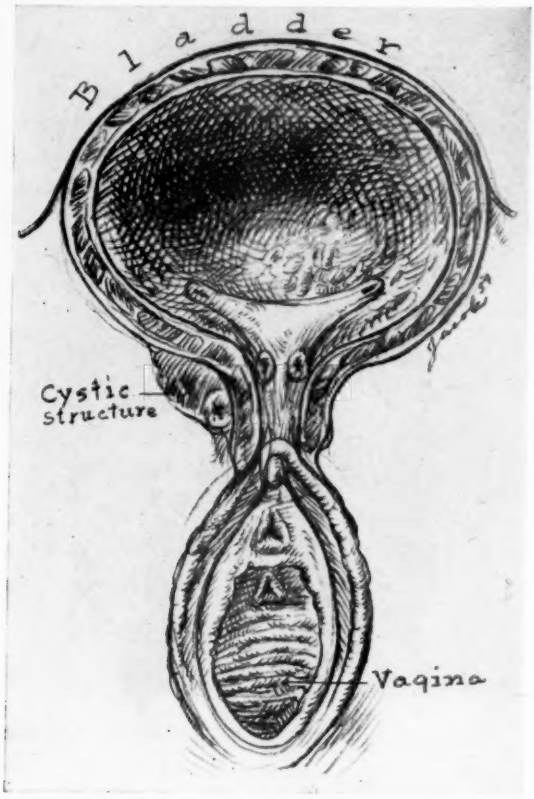


Fig. 6.—Composite diagrammatic representation of the ectopic orifices noted in this study.

In 4 out of 5 instances the ectopic ureters were catheterized (Fig. 6). In the first case, presenting as a cyst in the vagina, no orifice could be found and x-rays were obtained after needle puncture and aspiration.

The treatment which is entirely surgical must be completely individualized. The surgical steps were different in each of the 5 cases: (1) heminephrectomy and total ureterectomy, (2) heminephrectomy and partial ureterectomy, (3) nephrectomy, (4) heminephrectomy, total ureterectomy, and resection of intrabladder termination of ureter, and (5) partial ureterectomy.

Heminephrectomy will usually suffice when urinary incontinence without pyuria has been the problem. With pyuria, total ureterectomy may be necessary to relieve completely obstruction and eradicate a focus of chronic infection. Nephrectomy will be indicated to remove a useless organ. Partial ureterectomy certainly is not a procedure of choice. Where it is impossible to perform a heminephrectomy, the only way then to divorce the upper pole from the rest of the genitourinary tract, while maintaining the remaining normal portion of the kidney, is partial ureterectomy with as high ligation of ureter as possible. A similar situation was reported by A. B. Hepler.[8] To combine heminephrectomy and ureterectomy with transvesical resection of the submucosal portion of the ureter is most unusual. I have not seen it referred to in the literature. The terminal portion persisted as a pseudodiverticulum causing recurrent cystitis. It also acted as a cyst, causing obstruction at the neck of the bladder.

SUMMARY

1. Five cases of ectopic ureteral orifices in females have been presented.

2. Urinary incontinence was present in only one instance.

3. The most common and significant diagnostic criteria is the lateral displacement of the functioning portion of an enlarged kidney.

4. The treatment is entirely surgical and must be individualized in each instance.

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THE ROLE OF CLOSTRIDIA IN MORTALITY FOLLOWING AN EXPERIMENTAL WOUND IN THE GOAT

I. Quantitative Bacteriology

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BEGINNING with the standardization of the preparation by Ochsner and associates,[7] extensive physiologic studies have been made in these laboratories of an experimental wound in the goat. The preparation was developed with the prime intent of producing, in the laboratory, a state of traumatic shock which resembles the clinical state following severe injury more closely than do other experimental shock preparations, such as those based on graded hemorrhage, or closed muscle injury.

Briefly, the preparation is a large, open, bilateral hindquarter wound, produced by the detonation of high explosive. Untreated, the wound is uniformly lethal. Studies have been made of the effect of various experimental treatment measures. Certain of the previous studies[4, 5, 8] have indicated, by conclusion or implication, that: (1) the site of the lethal process is the open wound, (2) the nature of the lethal process is, at least in part, infectious, and (3) the offending organism is probably gram-positive, and, by inference from the response to various antibiotics, is somewhat more likely to be anaerobic than aerobic.

The circumstances are such as to support an indictment against the genus *Clostridium* and to warrant investigation designed to lead to either conviction or acquittal. Such was the genesis of these studies, which were made to test the following hypotheses:

A. If an infectious process is a significant determinant of mortality, then it should be possible to find evidence of some bacteriologic parameter which correlates with survival time.

B. If clostridia are the culprits, then data pertaining to clostridia should point to the presumed parameter more clearly than do data pertaining to other organisms.

C. Allowing for the elusive behavior of clostridial toxin in vivo, it should be possible to demonstrate the production of toxic material by clostridia in the wound, provided that the wound is truly the seat of the process and that clostridia are the offending organisms.

D. Allowing for the uncertain clinical efficacy of clostridial antitoxins, it should be possible to demonstrate some protective action of antitoxin, if clostridial toxins are being produced in the wound.

Received for publication Sept. 30, 1958.

MATERIALS AND METHODS

Animals.—All were castrated male Texas angora goats, 5 to 8 years old, weighing 30 to 50 Kg. The production of the wounds and the handling of the animals before and after wounding were as previously described.[4, 5, 8] Penicillin-treated animals received 0.6 Gm. (1,000,000 units) of penicillin G potassium intravenously every 3 hours.

Sampling of Wound Exudate.—At periodic intervals after wounding, samples of exudate were taken by a standard cotton-tipped applicator swab.* The sampling technique was to thrust and twist the swab into the muscle tissue in the wound area, and an attempt was made to avoid simply dipping into superficial pooled exudate.

The swabs were transferred to cold trypticase soy broth. On the basis of our own experience[2] and that of others,[9] we have accepted the average pickup and delivery of the swab sample in 0.9 ml. of broth to amount to a 10^{-1} dilution of wound exudate.

Estimation of Bacterial Concentration.—Quantitative estimations of wound flora were made on stained smears and on agar plates. The method of making these estimations will be published elsewhere.[2] In order to assure uniformity in the estimations, all smear estimations, and virtually all (99 per cent) of the plate estimations, were made by one individual.

Media and Incubation.—Plate estimations of bacterial concentration were made on four differential or selective media: MacConkey's agar† (gram-negative bacteria), mannitol salt agar† (staphylococci), SF agar‡ (fecal streptococci), and the blood azide egg yolk agar of Evans[1] (gram-positive anaerobes).

SF agar plates were incubated aerobically for 48 hours at 45° C. Evans' BAZY plates were incubated anaerobically in Brewer jars for 48 hours at 37° C. All other plates were incubated aerobically for 48 hours at 37° C.

Identification of Clostridia.—BAZY plates from two-thirds of the animals were studied for isolation and identification of species of *Clostridium,* using the key of Marshall and associates,[6] omitting the use of the methyl glucoside and glycerol reactions and reserving pathogenicity tests for use only when fermentation reactions were atypical. If a gram-positive anaerobic rod was found to be nonmotile, produced a stormy fermentation in milk and a positive lecithinase reaction, and generally followed the sugar fermentation pattern of *Clostridium perfringens,* it was accepted as *Clostridium perfringens* provided it proved pathogenic to guinea pigs.

EXPERIMENTAL

This study, the first in the series, was intended to test hypotheses A and B. Even if it neither supported nor controverted the hypotheses, it was expected to assist in characterizing the experimental preparation.

*Q-Tips, Inc., Long Island City, N. Y.
†Standard Products of Baltimore Biological Laboratory, Baltimore 18, Md.
‡Standard SF broth plus agar 30 Gm. per Liter.

TABLE I. MEAN BACTERIAL CONCENTRATIONS OF WOUND EXUDATES, UNTREATED AND PENICILLIN-TREATED ANIMALS

	PLATE ESTIMATIONS								DIRECT SMEAR ESTIMATIONS					
	SALT MANNITOL AGAR		MAC CONKEY'S AGAR		S. F. AGAR		EVANS' BAZY AGAR, L+		COCCI		G+ RODS		G− RODS	
H	0	P	0	P	0	P	0	P	0	P	0	P	0	P
4	4.05	3.36	3.63	3.32	3.94	3.16	2.85	1.94	3.93	3.50	4.08	2.90	3.87	3.20
	±.35	±.31	±.27	±.38	±.29	±.29	±.30	±.15	±.32	±.46	±.37	±.31	±.39	±.44
6.25	4.72	3.44	4.54	4.10	5.35	4.33	4.15	2.38	5.68	5.44	5.68	4.17	4.94	5.59
	±.21	±.30	±.28	±.28	±.28	±.30	±.39	±.12	±.22	±.26	±.28	±.38	±.40	±.35
9	5.82	4.10	5.50	5.50	6.29	4.80	6.50	3.48	6.75	5.75	7.03	5.64	6.54	6.48
	±.26	±.34	±.29	±.30	±.13	±.35	±.13	±.30	±.14	±.21	±.16	±.27	±.32	±.29
12	6.08	5.08	6.69	6.18	6.50	6.27	6.82	4.66	7.11	6.57	7.55	6.85	7.06	7.57
	±.21	±.43	±.19	±.42	±.10	±.22	±.10	±.60	±.15	±.41	±.22	±.28	±.19	±.26
16	6.80	5.50	7.03	6.77	6.88	6.44	7.02	5.37	7.82	6.83	8.09	7.04	7.50	7.29
	±.11	±.31	±.10	±.08	±.11	±.30	±.09	±.39	±.13	±.16	±.15	±.18	±.15	±.18
25	6.88	6.40	7.41	7.18	6.83	6.50	7.14	6.83	8.15	7.87	8.41	7.77	7.67	8.44
	±.14	±.13	±.09	±.08	±.17	±.40	±.14	±.12	±.16	±.15	±.15	±.16	±.19	±.11
49	--	6.43	--	7.31	--	7.37	--	6.87	--	8.40	--	8.18	--	7.89
	--	±.26	--	±.13	--	±.12	--	±.16	--	±.26	--	±.12	--	±.11

H = Hours after wounding.
0 = Untreated animals.
P = Penicillin-treated animals
Figures = Mean $\log_{10}$ of estimated bacterial concentration. ± standard error of mean.
G+ = Gram positive.
G− = Gram negative.
L+ = Lecithinase positive.
Mean Survival Time and Standard Error of Mean—no treatment = 21.33 ± 1.47 n = 36; penicillin treated = 37.58 ± 3.24 n = 36.

Basically, the study is a comparison of the quantitative bacteriologic findings in untreated animals and in animals treated with an effective antibiotic. Penicillin was chosen as the test antibiotic. It does not prolong the life of the experimental animal as long as do certain other antibiotics.[4, 8] The choice was one of convenience and economy.

Serial samples were taken of the wound exudates of the animals under study. Quantitative estimations were made of the concentrations of various types of organisms in the exudates. The data for untreated animals and penicillin-treated animals were compared.

RESULTS AND DISCUSSION

Results are summarized in Table I.

The mean survival time of untreated animals in this series (21.3 hours) is comparable to that obtained in previous studies.[7, 8] For penicillin-treated animals, the mean survival time is somewhat lower (37.6 hours). During the past 2 years there has been a slow but steady decline in the survival time of penicillin-treated animals in this laboratory. During the 4-month period covering this study the decline was more pronounced; the first 12 penicillin-treated animals survived for a mean of 47 hours, the last 12 for a mean of only 28 hours. The probable cause of the decline in survival time is discussed in greater detail elsewhere.[3] The decline was uncomplainingly accepted—in fact, the assumed contributing cause was jealously preserved in status quo—since the purpose of the study was not to appraise experimental treatment, but to seek a factor which correlates with survival time. For this latter purpose, variation in the survival time of treated animals is not undesirable.

Selected comparative "growth" curves for the various types of organisms studied are illustrated in Fig. 1. As would be expected, penicillin appears to have relatively little effect on the growth (increasing concentration) in the exudate of gram-negative organisms. For gram-positive organisms generally, penicillin appears to slow the rate of increase in concentration, or to delay it. For practical purposes, under the conditions of this study, the descriptive term "lecithinase-positive" is virtually synonymous with clostridia, at least in terms of quantitative estimations to nearest $\log_{10}$. There are other organisms which will grow anaerobically and produce a positive lecithinase reaction on the Evans' BAZY plate. However, the reaction usually has an atypical appearance. In the course of picking colonies for identification, we have rarely (less than 1 time out of 100) encountered colonies of such organisms in this study.

From 48 BAZY plates showing lecithinase-positive reactions, *Clostridia perfringens* was identified in every instance. Four specimen plates, which were made from early exudates from penicillin-treated animals and which showed no lecithinase activity, showed no clostridia. From 8 of the 48 plates, *Clostridia novyi* was isolated in addition to *Clostridia perfringens;* it was never found alone.

There were occasional identifications of other clostridia, including: *Clostridium aerofetidum, Clostridium capitovalis, Clostridium sporogenes,* and *Clostridium multifermentans. Clostridium septicum* was isolated from only 2 animals in this series.

Of the 72 animals in the study, all but 3 animals had plate estimations of clostridia, identified as *Clostridium perfringens,* of 10^6 or higher per milliliter at some time before death. The three excepted animals died at 5.2, 7.0, and 5.7 hours, and their highest plate estimations were 10^3 clostridia.

The effect of penicillin on the growth curves in Fig. 1 is evidently more pronounced on the staphylococci and on the clostridia. On the grounds of the lethality of the two genera in wound infections, it is tempting to attach more importance to the effect of penicillin in suppressing clostridia than to the effect on staphylococci. Even so, the significance of such an observation is not manifest from inspection of these curves; both curves in each pair are similar in shape, and are separated by a horizontal (time) distance of only 4 to 12 hours.

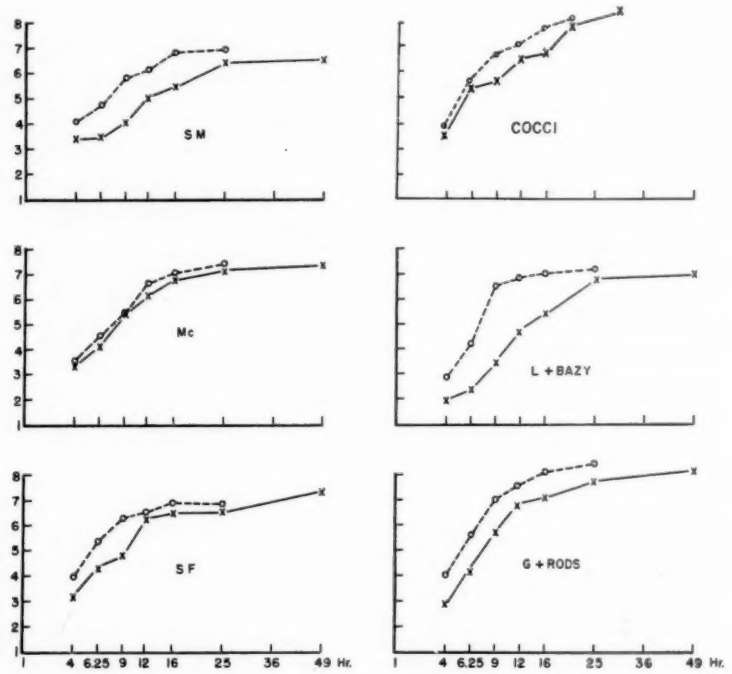

Fig. 1.—Comparative growth curves of various types of organisms, based on serial sampling of wound exudates. Ordinate: mean $\log_{10}$ of bacterial concentration per milliliter. Abscissa: time of sample after wounding, plotted as square root of hours. O----O: Untreated animals. ×——×: Penicillin-treated animals. SM: Salt mannitol agar. Mc: MacConkey's agar. SF: fecal streptococci agar. L + BAZY: lecithinase-positive colonies on Evans' agar. G + RODS: gram-positive rods. All data from dilution-streaked surface plate estimations except cocci and G + RODS, from stained smear estimations.

The discrepancy between such a limited time separation and a more marked separation in survival times in the two groups of animals was pointed out by Oppenheimer and associates[8]; in explaining this discrepancy they offered the hypothesis that the wound and the initial blood loss caused an immediate loss in host resistance, which was regained, under penicillin protection but not in untreated animals, at about 18 hours.

A simpler explanation of this apparent discrepancy is patent when the curves are plotted on an arithmetic rather than logarithmic ordinate (Figs. 2 through 8). A vertical (concentration) difference of 1 log on a curve in Fig. 1

represents ten times as many organisms, and this increment in organisms multiplied by a relatively short lag in hours may produce a quite different comparison between the quantities of organisms involved in the two groups of animals.

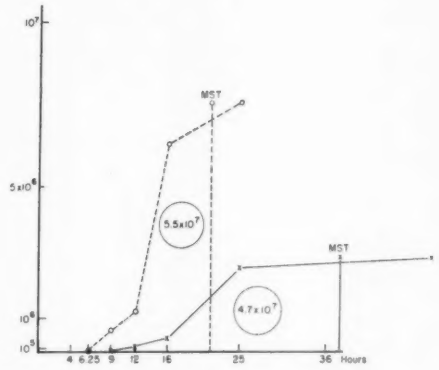

Fig. 2.

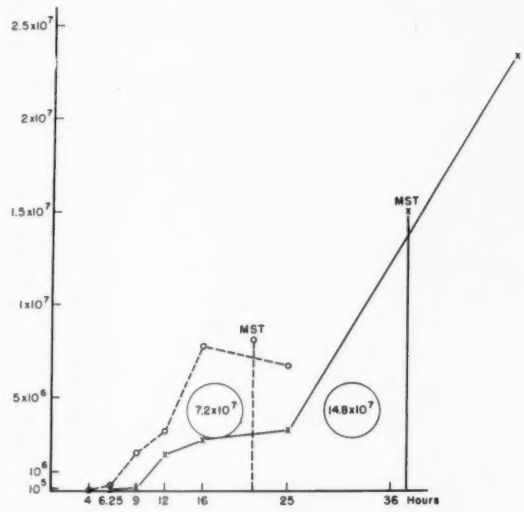

Fig. 3.

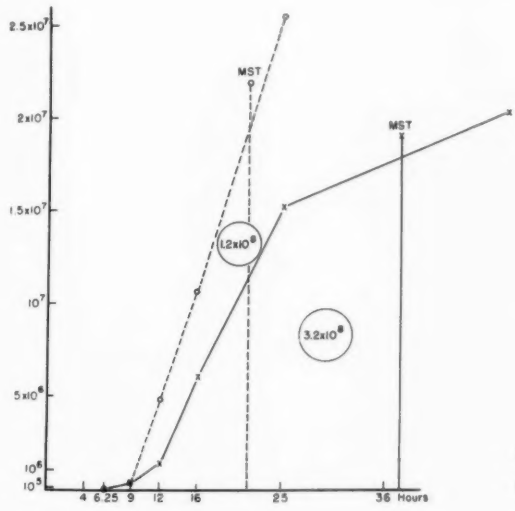

Fig. 4.

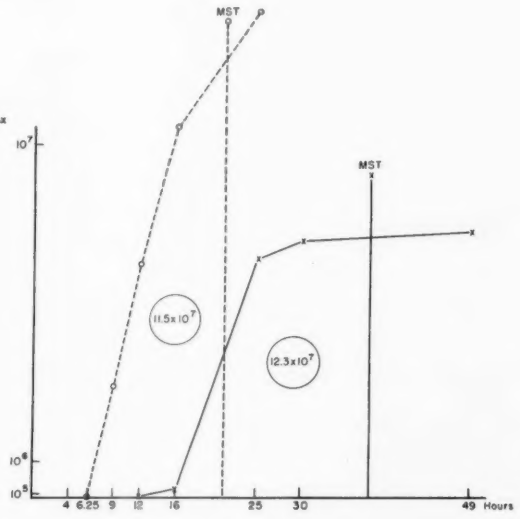

Fig. 5.

Figs. 2-5.—Comparison of cumulative organism-hour "dose" of various types of organisms in animals treated with penicillin and in untreated animals. Fig. 2, staphylococci (salt mannitol plate). Fig. 3, fecal streptococci (fecal strep. plate). Fig. 4, gram-negative rods (MacConkey's agar plate). Fig. 5, lecithmase-positive anaerobic organisms (Evans' BAZY plate). Ordinate: bacterial concentration per milliliter, arithmetic scale. Abscissa: time of sample after wounding, in hours, arithmetic scale. Circled figures: cumulative organism-hour per milliliter "dose" represented by area delimited by curve of concentration and mean survival time. MST: mean survival time. O----O: Untreated animals. ×——×: Penicillin-treated animals. Figs. 2-5, data from dilution-streaked surface plate estimations.

If growth of bacteria in the wound is a determinant of mortality of the animal, it is reasonable to expect the cumulative "dose" of organisms (concentration × time) to be relatable to survival time. Figs. 2 through 8 are graphic

expressions of such a "dose": organism-hours per milliliter of wound exudate. Since the wounds in both groups of animals are of exactly comparable size, the "per milliliter" factor is a constant, and comparison can be made between cumulative organism-hours at time of death in untreated animals and penicillin-treated animals.*

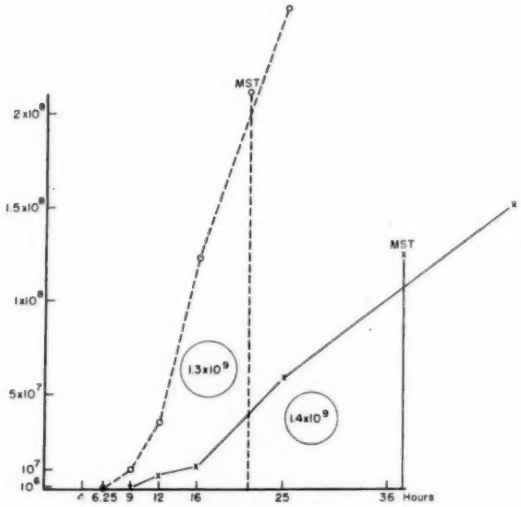

Fig. 6.

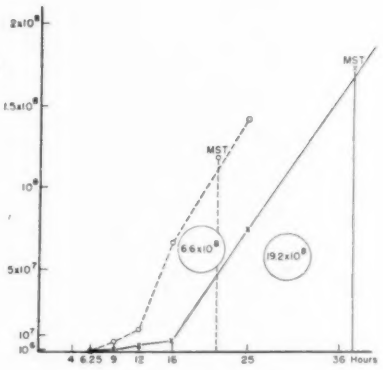

Fig. 7.

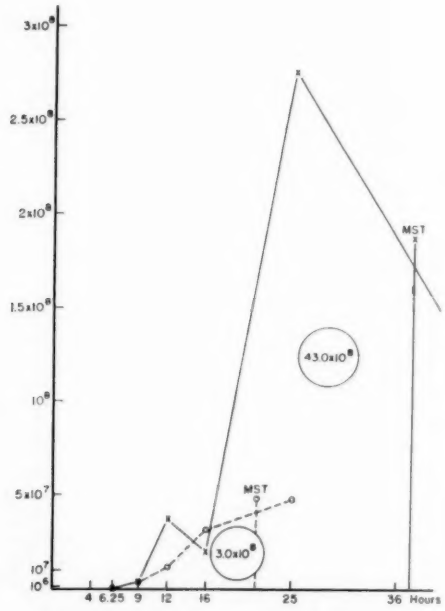

Fig. 8.

Figs. 6-8.—Data from stained smear estimations. Fig. 6, gram-positive rods (direct smear). Fig. 7, cocci (direct smear). Fig. 8, gram-negative rods (direct smear).

*Data from the earliest animals in this study were presented in Fed. Proc. 17: 98, 1958. Since that time, a better calibration of the plate counting technique has resulted in lower absolute "dose" figures, but the relation between the figure in treated and untreated animals remains the same.

It is evident that the data from direct counts of cocci and gram-negative rods (Figs. 7 and 8) and the data from plate estimations of fecal streptococci and gram-negative organisms (Figs. 3 and 4) do not support an hypothesis that these types of organisms are determinants of mortality which are common to both treated and untreated animals. It would appear that the dose of these organisms which the animal receives during life following wounding is an incident of survival time, not a cause.

The data for plate estimations of staphylococci (Fig. 2), plate estimations of clostridia (Fig. 5), and direct smear estimation of gram-positive rods (Fig. 6) do tend to support a hypothesis that organisms of these types may be determinant of survival time.

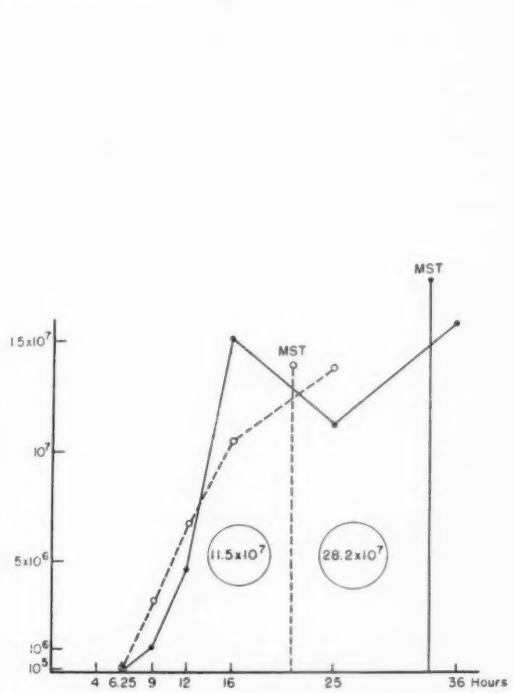

Fig. 9.

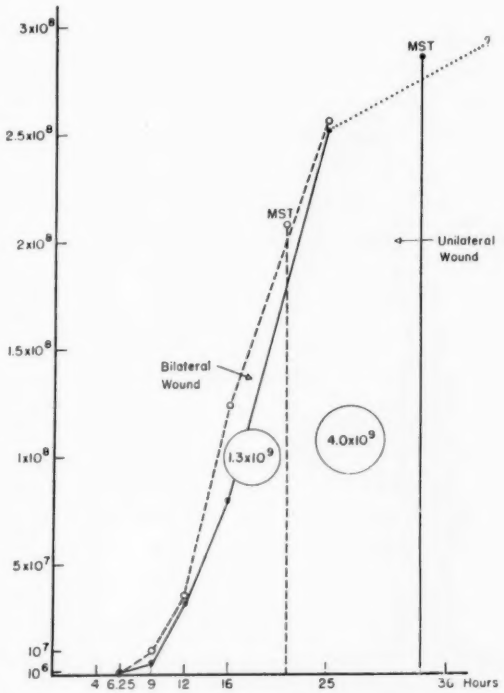

Fig. 10.

Figs. 9 and 10.—Comparison of cumulative organism-hour "dose" of selected types of organisms in untreated animals wounded in one leg and in both legs. Fig. 9, lecithinase-positive anaerobic organisms (Evans' BAZY plate). Fig 10, gram-positive rods (direct smear). Ordinate, abscissa, and abbreviations same as in Figs. 2-8. O----O: Bilateral wound. O——O: unilateral wound.

We are inclined to consider the relation of staphylococci to be one of coincidence rather than causation, for the following reasons:

1. On analysis of data from successive groups of 6 to 12 animals during the course of the study, the staphylococcal dose relationship has been found to be variable. At times, penicillin-treated animals have shown an organism-hour tolerance twice as high as untreated animals; at other times the ratio is reversed. The relationship between the clostridial organism-hour dose in untreated animals and penicillin-treated animals remained steady throughout the study within the range of 1:1 to 1:1.3.

2. Correlation coefficients between bacterial concentration at a given hour and the survival time of the animal from which the sample is taken are generally of a very low order of significance ($P = >0.1$; rarely $P = <0.05$). However, for staphylococci, approximately one-half the coefficients for the various sampling hours are *positive;* all correlations for clostridia are *negative* except a correlation of +0.031 for penicillin-treated animals at 12 hours after wounding ($P = >0.9$).

3. A priori, one would attach more significance to the finding of 12,000,000 clostridia per milliliter in a wound than to the finding of 5,000,000 staphylococci (interpolated mean concentration at time of death, untreated animals).

If the organism-hour figure for clostridia is indicative of a true parameter of lethality, the figure should show a logical response to the introduction of variables other than those affecting concentration (effect of penicillin). The effect of clostridial antitoxins, in permitting the animals to survive a larger dose of clostridial organisms, is presented elsewhere.[3] Another means of testing the relationship is to vary the "per milliliter" constant. When an animal is wounded in one leg only, he does not live twice as long, but he does live long enough to receive twice as great (or greater) dosage of clostridia in terms of organism-hours per milliliter (Figs. 9 and 10).

SUMMARY

In a standardized, high-explosive wound in the goat, developed for the study of traumatic shock, both untreated animals and penicillin-treated animals die with wounds of the same size, at a time when they have sustained approximately 1.2 by 10^8 *Clostridium perfringens* organism-hours per milliliter of wound exudate. The data are not sufficient to support a conclusion as to the role of clostridia in mortality in this preparation, but they tend to further incriminate *Clostridium perfringens* as a significant determinant of survival time, common to both treated and untreated animals.

We as individuals are solely responsible for the data, opinions, and conclusions herein, which are not to be construed as reflecting the position of the United States Army or any organizational element thereof.

We are deeply grateful for the information, advice, and assistance provided by: Lieutenant Colonel William H. Moncrief, Lieutenant Colonel Hinton Baker, Major Roger Sherman, Dr. Stanley M. Levenson, and Sergeant First Class Joseph F. Miller, Walter Reed Army Institute of Research; and Dr. Carl M. Herget, Privates First Class Floyd Brinkley, Bernard Ondash, Dwight Pence, and Ronald Koch, Mr. John Sinsko, and Mr. David Ewing, Chemical Warfare Laboratories.

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THE ROLE OF CLOSTRIDIA IN MORTALITY FOLLOWING AN EXPERIMENTAL WOUND IN THE GOAT

II. Demonstration of Toxic Materials in Wound Exudate

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IN THE preceding paper,[1] the emphasis was on determining the quantitative and qualitative bacterial flora of the wound. This paper is concerned with the tentative demonstration of clostridial toxins in the wound exudate.

The background for this phase of study was as follows: (1) the positive correlation of numbers of *Clostridium perfringens* and death of the goats reported in the previous paper,[1] and (2) the fact that guinea pigs invariably developed severe clostridial myonecrosis following intramuscular injection of unfiltered wound exudate from wounds of blasted goats.

MATERIALS AND METHODS

Animals.—The goats and techniques of wounding were described previously.[1] White Swiss mice, Bagg Strain, each weighing 18 to 20 grams and smooth-haired English-type guinea pigs weighing 250 to 300 grams were obtained from the Walter Reed Army Medical Center colony. Guinea pigs were prepared for intramuscular injection by a mild crushing of the gluteus muscle.

Antitoxin Administration.—Guinea pigs were injected intramuscularly with 0.5 ml. of commercial trivalent antitoxin or control serum† immediately prior to the injection of 0.5 ml. of unfiltered wound exudate. Mice were premedicated by intramuscular injection of antitoxin or control serum 24 hours prior to the intravenous administration of Seitz-filtered wound exudate.

Antibiotic Treatment.—The penicillin-treated goats were treated as described in the preceding paper.[1]

RESULTS

It was shown that guinea pigs invariably developed a severe myonecrosis following the injection of exudate from goat wounds. While it seemed apparent that these guinea pigs were dying from clostridial myonecrosis, all of the species of bacteria occurring in appreciable numbers in the wound were

Received for publication Sept. 30, 1958.

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†Obtained through the courtesy of Dr. I. S. Danielson, Lederle Laboratory Division, American Cyanamid Co., Pearl River, N. Y.

isolated and guinea pigs were injected with pure cultures of the following: *Escherichia coli, Streptococcus fecalis, Staphylococcus aureus,* and *Clostridium perfringens.* Only those animals injected with *Clostridium perfringens* died, usually between 40 and 64 hours after injection as compared with 12 and 24 hours when the wound exudate containing all four was injected. The decreased survival time of the guinea pigs injected with the wound exudate was considered to be the result of synergism among the bacterial species or the presence of preformed toxins, or both.

Initially, the toxicity of wound exudate from an untreated goat was compared with exudate from a goat treated with penicillin. As might be predicted from the bacteriologic findings, the wound exudates from the untreated goat were more toxic, both in terms of earlier mortality and decreased survival times of the guinea pigs (Table I). In a similar experiment half of the guinea pigs were protected by the concurrent administration of trivalent gas gangrene antitoxin. The results in Table II show that all of the guinea pigs receiving antitoxin survived, while most of the unprotected guinea pigs injected with exudate from the control goat died. The 6 dead animals were cultured at autopsy and *Clostridium perfringens* was recovered from each animal. When these isolated cultures were subsequently injected into normal guinea pigs, all died within 4 days.

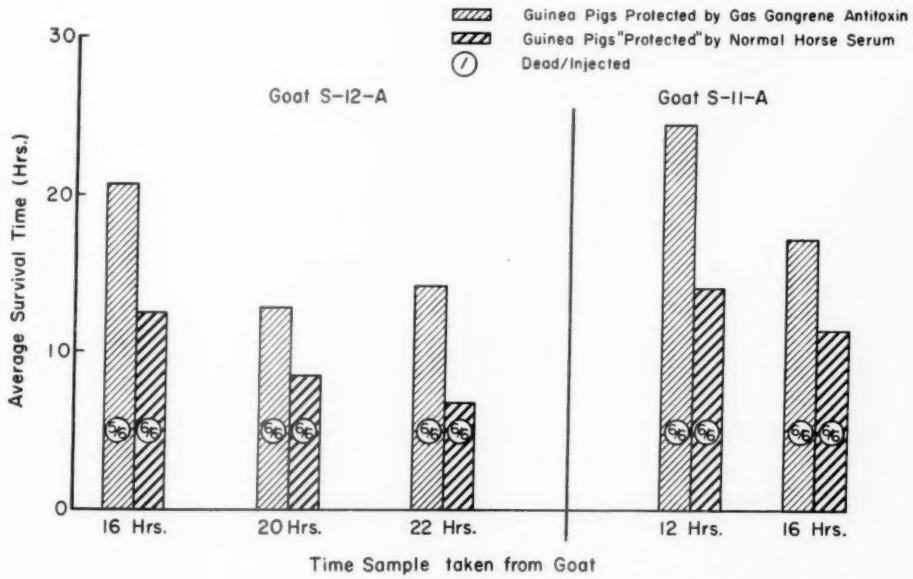

Fig. 1.—Survival time of guinea pigs injected with unfiltered exudate from the wounds of untreated goats.

In the next experiment samples of wound exudate from 2 untreated goats were injected into normal and antitoxin-protected guinea pigs. Both of these control goats had longer survival times and higher counts of *Clostridium perfringens* (10^8 to 10^9 ml.) than the goat in the preceding experiment. In Fig. 1, it can be seen that, while all but one of these animals died, survival time was prolonged in every group of guinea pigs premedicated with antitoxin.

The experiments described indicate that virulent clostridia were present in the wounds of these goats and that the lethality of the unfiltered wound exudate could be influenced by trivalent gas gangrene antitoxin.

TABLE I. MORTALITY OF GUINEA PIGS INJECTED WITH UNFILTERED EXUDATE FROM WOUNDS OF BLASTED GOATS

GOAT NUMBER	GOAT THERAPY	TIME OF SPECIMEN (HOURS AFTER BLAST)	DEAD/INJECTED	AVERAGE SURVIVAL TIME (HOURS)
1646	None	4	2/4	
1654	Penicillin	4	0/4	
1646	None	8	4/4	
1654	Penicillin	8	2/4	
1646	None	12	4/4	9.7
1654	Penicillin	12	4/4	23.2

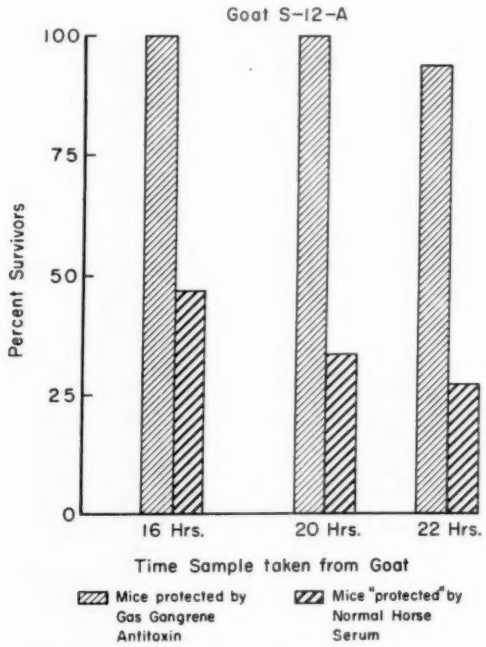

Fig. 2.—Mortality of mice injected with filtered wound exudate from untreated goats.

TABLE II. EFFECTS OF CONCURRENT INJECTION OF GAS GANGRENE ANTITOXIN ON LETHALITY OF WOUND EXUDATE IN GUINEA PIGS

GOAT THERAPY	TIME OF SPECIMEN (HOURS AFTER BLAST)	LECITHINASE-POSITIVE ORGANISM	CONCURRENT ANTITOXIN	DEAD/INJECTED
Penicillin	7	< 3	No	0/4
	7	< 3	Yes	0/4
	10	3	No	0/4
	10	3	Yes	0/4
None	7	6	No	2/4
	7	6	Yes	0/4
	8	> 6	No	4/4
	8*	> 6	Yes	0/4

*Time of death.

The next series of experiments were designed to show the presence of clostridial toxins in the wound itself. Preliminary studies showed that 0.5 ml. of Seitz-filtered wound exudate was not lethal for guinea pigs, so mice were selected as the assay animal. The results in Fig. 2 represent 30 mice per group. It can be seen that practically all of the mice premedicated with antitoxin survived while only 25 to 50 per cent of those premedicated with normal serum survived. In a subsequent experiment 4 control goats were used so that each wound was sampled only one time. This was done to preclude changes in flora resulting from "cleaning" the wound to obtain exudate. In Fig. 3, it can be seen that lethal amounts of toxin appeared in the wound about 12 hours postblast and enough had accumulated by 20 hours postblast to kill some of the antitoxin-protected mice.

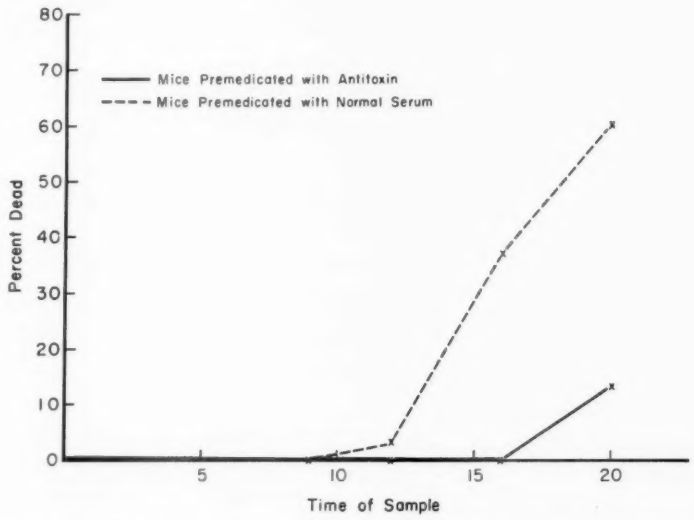

Fig. 3.—Mortality of mice injected with filtered wound exudate from untreated goats.

DISCUSSION

While the experiments just described indicate that there are clostridial toxins in the wound, there is no proof that the toxins are absorbed into the circulation of the goat. No technique is available for the detection of clostridial toxins in vivo, but it has been shown that I^{131}-tagged human serum albumin is readily absorbed from these goat wounds.[3] The likelihood that shock-producing toxic materials are elaborated in anoxic muscle was studied by Pope and associates,[2] who obtained fluid from the legs of dogs subjected to tourniquet shock for 5 hours and injected this fluid intravenously into recipient dogs. The toxicity of the fluid for the recipient dogs could be correlated to the number of clostridia present. In a subsequent group, the dogs were injected with a pure culture of *Clostridium sp.* just before ligation of the muscle and the bacteria were allowed to incubate in vivo throughout the ischemic period. The fluid collected at the end of the ischemic period was toxic for dogs and mice, and it was possible to protect a dog by the prior administration of gas gangrene antitoxin.

The inoculum of Clostridia in this study is assumed to be the skin and hair at the blast site, because it has been shown that the unimpaired muscle of goats is free of bacteria. Thus the requirements for clostridial myonecrosis, that is, inoculum, damaged tissue, and impaired blood supply, are present immediately after blast and in many instances the survival time of the goat can be related to the proliferation of *Clostridium perfringens.*

It is not to be inferred that Clostridia and their toxins are the sole cause of death in these goats. Among other variables, undoubtedly, the loss of blood is a contributory factor. We have shown that the tolerance of rats* subjected to sublethal hemorrhagic shock (40 mm. Hg for 2 hours) to a sterile filtrate derived from *Clostridium perfringens* was decreased as evidenced by the fact that the LD_{50} of the filtrate changed from 1.4 ml. in nonshocked rats to 0.7 ml. in shocked rats. Thus the possibility must be considered that the blasted goat is more susceptible to clostridial toxins because of its blood loss.

SUMMARY

1. Lethality of unfiltered wound exudates for laboratory animals is related to virulent *Clostridium perfringens.*

2. Toxic materials in wound exudates can be mitigated by commercial trivalent gas gangrene antitoxin.

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*We are indebted to Mr. William Galvin and Mr. Richard Nesti for the preparation of these rats.

THE ROLE OF CLOSTRIDIA IN MORTALITY FOLLOWING AN EXPERIMENTAL WOUND IN THE GOAT

III. Effect of Clostridial Antitoxin in Prolonging Survival

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IN THE preceding papers dealing with a standardized, uniformly lethal, high-explosive wound in the goat, we have presented data which: (1) suggest a dosage-response relationship between concentration of clostridia in the wound and survival time, in untreated animals and penicillin-treated animals,[4] and, (2) demonstrate the presence of clostridial toxins in the wound exudate in both untreated animals and penicillin-treated animals; the toxin appears later and in lower concentrations in the treated group.[7]

If clostridia are growing in and producing toxin in the wounds of these animals, it is possible that treatment with specific clostridial antitoxins would result in prolongation of survival time. The choice of the word "possible" is deliberate and not simply a matter of exaggerated reserve in postulation. The known and titratable effectiveness of antitoxin in neutralizing toxin in vitro and the demonstrated presence of toxigenic clostridia in the wound in numbers which bear an apparent relationship to survival time do not add up to a simple "If . . . since . . . therefore . . ." hypothesis on the effectiveness of clostridial antitoxin in prolonging survival time.

In the treatment of clinical clostridial infections, antitoxin has not been a brilliant success. It is still in favor with British and French surgeons, but many American surgeons are quietly discarding it. There is very little positive evidence supporting the existence, in clostridial infections of muscle, of a true clostridial toxemia, that is, specific clostridial exotoxins circulating in the blood. On the contrary, there is some indication that the systemic "toxemic" effects of clostridial infections of muscle are mediated through secondary effects of the local action of specific toxins on tissue.[5, 6] The implication is that a given quantity of antitoxin might be more effective if localized in and around the wound area than if distributed in the general circulation.

Preliminary experiments were performed on 24 animals: 12 untreated, 6 treated with intravenous antitoxin, and 6 treated with antitoxin injected intramuscularly in and around the wound area. These preliminary experiments were followed by sequential probability ratio testing.[2] The

Received for publication Sept. 30, 1958.

series was too limited to be statistically conclusive in itself,* but it gave indication that we might expect to obtain statistically significant results more readily through the use of locally injected antitoxin than by the use of intravenous antitoxin. Since our supply of antitoxin was limited and since this was a diagnostic and not a therapeutic study, the use of antitoxin in further experiments was limited to local intramuscular injection.

It is interesting to note that the first recorded administration of *Clostrium perfringens* antitoxin, reported in this Journal 40 years ago,[1] was an intramuscular injection in and around the site of the experimental infection.

MATERIALS AND METHODS

The animals and the method of wounding were as described previously.

Sterilization of Instruments.—In the first paper[4] we described a progressive decline in survival time of penicillin-treated animals during these studies. The consensus of suspicion of the laboratory staff was directed toward contamination of the clamps utilized for hemostasis; these clamps were scrubbed thoroughly after use but were not sterilized. During Series I of these experiments this regime of "clean but not sterile" was continued; during Series II hemostats were autoclaved immediately before use.

Antibiotic Treatment.—During Series I, penicillin was administered by intermittent intravenous injection every 3 hours: 0.6 Gm. (1,000,000 units) of penicillin G potassium. During Series II, penicillin was given by intramuscular injection, approximately one hour before wounding, immediately after wounding, and every 8 hours thereafter: 0.2 Gm. of procaine penicillin G potassium and 0.6 Gm. of crystalline penicillin G potassium.

Antitoxin Treatment.—The contents of 10 vials of commercial trivalent clostridial antitoxin were diluted to 1 L. with normal saline, and 500 ml. was injected into each hindquarter in the gluteus, quadriceps, and hamstring muscle groups. Injections were completed approximately one hour before wounding. Each vial of antitoxin, a so-called "therapeutic dose," was labeled to contain: 9,000 units of *Clostridium perfringens* antitoxin, 9,000 units of *Clostridium novyi* antitoxin, and 4,500 units of *Clostridium septicum* antitoxin. All antitoxin used was the product of a single manufacturer, from a lot prepared less than 5 months before use. The average fluid content of the vials was 12 ml. Paper electrophoretic curves showed the protein content to be globulin; the concentration was 17.0 Gm. per cent.

Control Serum Treatment.—As a control for the effect of injection of such quantities of saline and globulin, a number of animals were injected before wounding with a saline dilution of concentrated serum, processed from

*Even after a series involving 46 antitoxin-treated animals, the validity of the differences was disappointing. In comparison with untreated animals, animals treated with locally injected antitoxin showed a suggestively significant increase in survival time ($p<0.05$). Intravenous antitoxin produced a slight but statistically insignificant increase in survival time; this limited effect of intravenous antitoxin was sufficient to narrow the difference between the effect of local and intravenous antitoxin, so that an independent comparison of route of administration was not of statistical significance.[3]

slaughter-house horse serum by the same manufacturer and by the same methods as the antitoxin.* The electrophoretic curves for this material were identical to those of the antitoxin. The protein content was slightly less (15.4 Gm. per cent); the fluid volume of the processed serum was increased (to 130 ml.) in order to give the same globulin content (2.4 Gm. per cent) in the liter of solution injected.

RESULTS AND DISCUSSION

Results are summarized in Table I.

During Series I there was an even further reduction in survival time of penicillin-treated animals, as compared to the last third of the experiments reported in the first paper. There was, at the same time, an apparent decrease in the already marginally significant[3] effect of antitoxin when used as the sole treatment. After completion of Series I, two variables were introduced simultaneously: change in the dosage and route of administration of penicillin, and sterilization of the clamps.

TABLE I. EFFECT OF PENICILLIN AND ANTITOXIN ON SURVIVAL TIME

	TREATMENT				
	NONE	ANTITOXIN ALONE	PENICILLIN ALONE	PENICILLIN PLUS ANTITOXIN	PENICILLIN PLUS SERUM
Series I					
n	8	8	8	8	--
M. S. T.	20.23	22.25	31.47	33.59	--
S. E. M.	±1.99	±2.34	±4.27	±7.64	--
Series II					
n	11	11	11	11	11
M. S. T.	21.08	25.46	41.25	75.71	40.27
S. E. M.	±2.21	±3.00	±7.22	±8.58	±6.96

Series I = Hemostats not sterile; penicillin by intermittent intravenous injection.
Series II = Sterile hemostats; intramuscular penicillin.
n = Number of animals.
M. S. T. = Mean survival time.
S. E. M. = Standard error of mean survival time.

In comparison to Series I, every comparable group of animals in Series II showed a higher mean survival time, and in Series II the mean concentrations of clostridia per milliliter of wound exudate were lower (Fig. 1).† We interpret the effect of sterilization of the clamps to be interruption of the repeated transmission of a virulent strain of *Clostridium perfringens,* one which is better able to invade and establish growth in the wound. We prefer this interpretation to that of the interruption of the transmission of a penicillin-resistant organism. Tests of penicillin sensitivity revealed no differences between organisms isolated early in the series reported in the first paper, late in that series and in Series I of these experiments, and in Series II of these experiments.

*We are indebted to Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y., for this serum.

†An analysis of variance shows the survival time increases to be of no statistical significance; the decreases in clostridial concentration were significant (untreated animals, $p<0.05$ and penicillin-treated animals $p<0.01$).

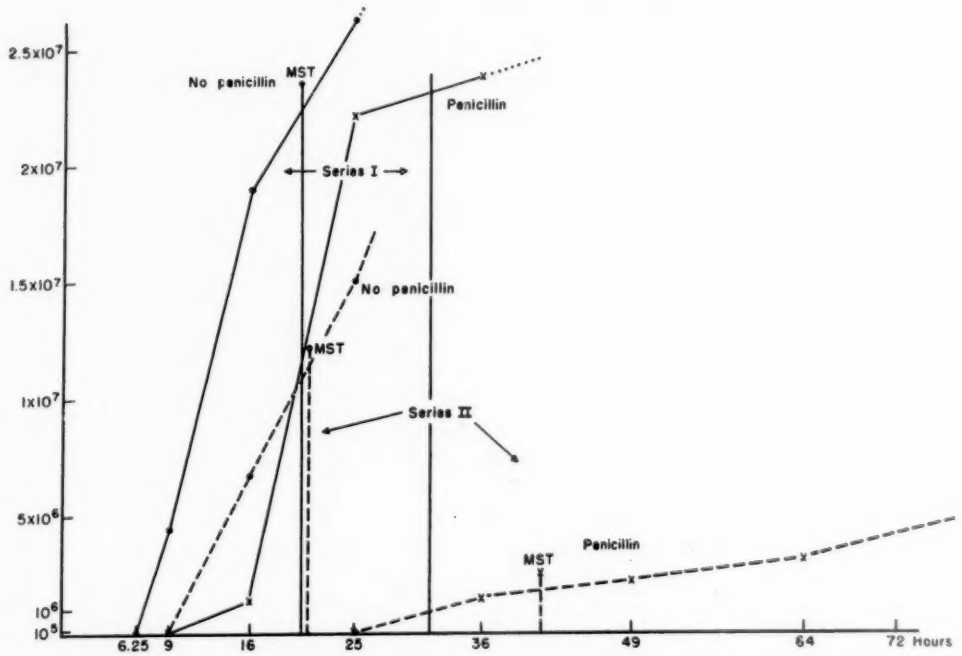

Fig. 1.—Estimated concentration of clostridia per milliliter of wound exudate, blood azide egg yolk surface plate estimations (Series I and II). M. S. T. = Mean survival time.

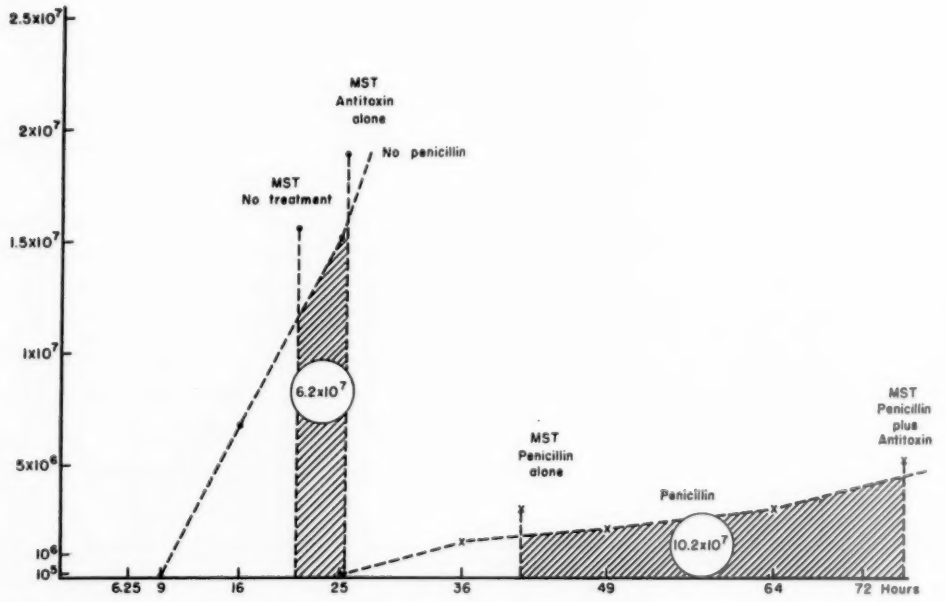

Fig. 2.—Comparative protection from antitoxin in terms of organism hours per millilter of wound exudate, blood azide egg yolk surface plate estimations; antitoxin alone and antitoxin plus penicillin (Series II). M. S. T. = Mean survival time.

The accuracy of this interpretation is not material to this study, which is an attempt to answer a single question: is clostridial infection a significant determinant of survival time in this preparation or is it not? For that answer we have utilized only Series II of these experiments, since the results with penicillin treatment in that series are more nearly consistent with previous extensive experience with this preparation. Series I appears to be atypical; it is associated with a studious and deliberate persistence in not sterilizing the instruments. Prior to the experiments reported in the first paper it has been the custom in these laboratories to sterilize the instruments at frequent, but irregular, intervals.

In Series II, the effect of antitoxin alone, even after local infiltration, was too limited to be of statistical significance in so small a series. However, when the survival time of penicillin-treated animals is used as the control or base line, the addition of locally injected antitoxin to the treatment regimen is associated with a highly significant increase in survival time (Table II). We consider the limited effectiveness of antitoxin alone and the greater effectiveness of antitoxin plus penicillin to be indicative of the fact that our dosage of antitoxin (2,000 units of *Clostridium perfringens* antitoxin per kilogram) was marginal. It is ineffective against clostridial infection of the extent and degree characteristic of the preparation. When the degree of infection (concentration of organisms) is cut down by the administration of penicillin, this limited dosage of antitoxin is more effective.

TABLE II. ANALYSIS OF VARIANCE, EFFECT OF ANTITOXIN ON SURVIVAL OF ANIMALS TREATED WITH PENICILLIN (SERIES II)

VARIANCE SOURCE	DEGREES OF FREEDOM	SUMS OF SQUARES	MEAN SQUARES	F	P
Between groups:					
C vs. AB	1	8,961	8,961	13.58	< 0.001
A vs. B	1	5	5	131.9	< 0.9
Within groups:					
(Error)	30	19,794	659.8		
Total	32	28,760			

A = Penicillin alone.
B = Penicillin plus processed serum.
C = Penicillin plus antitoxin.
F = Variance ratio.
P = Probability that difference between groups compared is due to chance alone.

Quantitatively, a general relationship appears to hold true with reference to the capacity of this limited dose of antitoxin to protect the animal against the effect of the infection: in animals otherwise untreated, antitoxin appears to be "worth" about 6×10^7 organism hours per milliliter of wound exudate in terms of protection; in penicillin-treated animals it is "worth" a comparable amount of protection (approximately 10×10^7 organism hours per milliliter), but this amount of protection translates into a 35-hour gain in survival time, as against a 5-hour gain in animals not treated with penicillin (Fig. 2).

In comparison with Fig. 5 in the first paper, there is a marked discrepancy in the cumulative clostridial dose at time of death in animals treated with penicillin alone (Fig. 1). This is perhaps explainable by the work of Wise,[8] done in parallel with these studies; the mechanism of death in these animals appears to be a combined effect of progressive loss in circulating blood volume, plus clostridial infection. Either is sufficient alone to kill the animal. During the long period of suppression of clostridial count in the Series II penicillin-treated animals (over 30 hours before the count exceeds 10^5 per milliliter), the animals may be slowly approaching death from trauma alone or trauma with minimal superimposed infection. If such is the case, it may be that only a short period of more active infection is sufficient to bring the course to fatal termination.

SUMMARY

The previous papers have suggested a relation of the concentration of clostridia in the wound to survival time in an experimental wound in the goat and demonstrated the presence of clostridial toxins in the wound exudate. The present paper demonstrates that an otherwise marginally effective dosage of clostridial antitoxin, when administered by local infiltration in combination with penicillin treatment, results in a highly significant prolongation of survival time.

CONCLUSION

In an open wound preparation in the goat, which has been previously studied extensively as a preparation of experimental traumatic shock, clostridial infection in the wound is a significant determinant of survival time.

The authors as individuals are solely responsible for the data, opinions, and conclusions herein, which are not to be construed as reflecting the position of the United States Army or any organizational element thereof.

We are deeply grateful to Dr. J. D. MacLennan for information and advice, and to Colonel A. R. Dreisbach, Dr. D. B. Dill, and Dr. Caroline Tum-Suden for confidence, encouragement, and support.

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EFFICACY OF PLASMA AND DEXTRAN COMPARED TO SALINE FOR FLUID REPLACEMENT FOLLOWING TOURNIQUET SHOCK

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TOURNIQUET shock is characterized by the phenomena of hemoconcentration and diminished circulating volume.[6, 7] The fluid which accumulates in the injured limbs[2, 4] makes unusually large amounts of intravenous saline necessary to prevent death in animals subjected to a tourniquet trauma which is lethal to untreated animals.[1, 8, 10, 15]

It is generally held that the role of the saline replacement is twofold: to maintain circulating fluid volume and to allow a greater fluid accumulation in the injured areas than would take place if circulating volume were not maintained.[11] Maintenance of circulating volume apparently is of prime importance in overcoming the lethality of the trauma, the extra fluid loss into the limbs being secondary to it.

The infusion of plasma has been shown to be more efficacious as a fluid therapy than saline following tourniquet shock when given in prolonged intermittent fashion.[9, 10] However, when given soon after tourniquet release, plasma has been found to be no more effective than equal amounts of normal saline.

It has also been reported[4] in traumatic shock in dogs that plasma is much more effective when administered over a period of hours than when given in a single dose, and that plasma and saline are equally effective in single doses, but plasma is superior to saline when given in multiple doses.

In order to evaluate the relative effectiveness of plasma and plasma-expander substances, conditions were first established, using an otherwise lethal tourniquet trauma, for comparisons of the therapeutic capacities of different volumes of isotonic sodium chloride solution. Effectiveness was reflected in survival. In the course of this evaluation, comparisons were also made between saline and plasma and between saline and dextran. Since dextran is commercially available in both normal saline and dextrose in water, both preparations were compared to saline as replacement therapy in tourniquet shock.

Although there is an extensive literature regarding the efficacy of saline therapy following tourniquet shock, the reports of the methods of administration are generally crude. The rapid infusions of large amounts of saline, if

Supported by Department of the Army, Office of the Surgeon General, Contract No. DA-49-007-MD-799.

Received for publication Oct. 25, 1958.

not particularly deleterious, may not be as beneficial as more critical administration over the periods of greatest loss of circulating volume.

Tabor,[16] Millican[10] and their co-workers and Koletsky and Gustafson[5-8] have shown that, with use of intermittent intraperitoneal and intravenous infusions or rapid continuous intravenous infusions, maximum protection is achieved at volumes between 15 and 18 per cent of the body weight. It would seem that the more physiologic nature of slow, constant intravenous infusions might achieve higher survival rates at significantly lower total infusion volumes. This objective was achieved.

METHODS

Male albino rats of the Holtzman Farms, weighing between 200 and 250 grams, were used. Each animal was individually housed in an air-conditioned laboratory for at least 4 days prior to use. Food was removed from the cages approximately 15 hours before the application of tourniquets.

Animals were weighed to the nearest half gram and anesthetized with sodium pentobarbital (Nembutal) intraperitoneally (30 mg. per kilogram of body weight). Tourniquets were then applied to both hind limbs in a standardized manner.

No. 10 Eberhard-Faber rubber bands were used as tourniquets. A single band was turned evenly five times over the end of an open, thin glass tube, measuring 21 mm. in outside diameter and 4 inches in length. The lower extremity was drawn into the glass tube by an 8-inch string, loosely tied around the lower hind leg, and dropped through the tube. Using the string for traction, the tube was pushed as high on the thigh as possible and the band slipped off the tube onto the thigh. The teeth of the animals were then clipped short to prevent them from biting either their legs or the tourniquets after awakening.

Varying time intervals of tourniquet application were used in pilot studies to establish a consistently lethal trauma. The application of tourniquets in this manner for 4½ hours has been found to be such a trauma (Table I), and has been used in all experiments herein reported.

At the time of tourniquet release, the animals were again anesthetized by an intraperitoneal injection of a mixture of Nembutal and barbital (15 mg. Nembutal and 100 mg. barbital per kilogram of body weight). After anesthesia was re-induced, the right jugular vein was isolated. To facilitate the dissection and maintain maximum dilatation of the vein, 0.4 c.c. of 2 per cent procaine was injected into the area prior to isolation.

One hour after tourniquet release the vein was cannulated with a small polyethylene tube, which was connected to a syringe in the constant infusion pump and fluid administration started. Aqueous penicillin G (500 units per cubic centimeter) was added to the solution, since sterile equipment and technique were not used. The delivery time of the infusion was regulated to 3 hours ± 9 per cent. After the prescribed infusion was completed, the vein was ligated and the neck closed with skin clips. One to three constant infusion pumps, each housing 12 syringes, were used.

TABLE I*

AMOUNT OF SALINE (C.C./100 GRAMS BODY WEIGHT)	24 HOURS AFTER REMOVAL OF TOURNIQUET			48 HOURS AFTER REMOVAL OF TOURNIQUET		
	LIVED	DIED	SURVIVAL (%)	LIVED	DIED	SURVIVAL (%)
0						
Pooled results	16	262	5.8	6	272	2.2
3	2	8	20.0	1	9	10.0
	4	5	44.0	1	8	11.0
	12	7	63.0	8	11	42.0
Pooled results	18	20	47.4	10	28	26.3
5	8	1	89.0	8	1	89.0
	6	4	60.0	3	7	30.0
	8	3	72.0	6	5	54.0
	5	3	62.5	2	6	25.0
	7	1	87.5	5	3	62.5
	7	1	87.5	6	2	75.0
	17	3	85.0	10	10	50.0
Pooled results	58	16	78.4	40	34	54.1
7	5	2	71.4	4	3	57.1
	6	2	75.0	5	3	62.5
	7	1	87.5	6	2	75.0
	19	4	82.7	19	4	82.7
Pooled results	37	9	80.4	34	12	73.9
9	22	2	91.7	18	6	75.0
	19	5	79.2	15	9	62.5
	20	2	90.9	19	3	86.4
Pooled results	61	9	87.1	52	18	74.3
15	12	0	100.0	12	0	100.0
	5	1	83.0	5	1	83.0
	6	0	100.0	6	0	100.0
Pooled results	23	1	95.5	23	1	95.5

*Survival of rats subjected to a lethal application of bilateral tourniquets and infused with varying amounts of normal saline over a 3-hour period, one hour after release of tourniquets.

Small supplemental amounts of intraperitoneal Nembutal were given if an animal appeared too restless. After skin closure the animals were returned to their cages where food and water were available to them.

Survival was recorded at 24 and 48 hours after tourniquet release in all groups.

Controls.—Control animals were originally treated in an identical manner to the experimental groups, except for infusion. As the experiments progressed, it was observed that the mortality was unaffected if the jugular vein was not exposed and ligated (Table I). Therefore, control animals were reanesthetized when the tourniquets were released and simply returned to their cages.

To measure any mortality rate inherent in the surgical manipulations and infusion, a group of 20 animals which had not been subjected to tourniquet

application was treated in otherwise the same manner and infused with 7 c.c. of normal saline per 100 grams of body weight.

Survival Following Graded Saline Infusion.—Amounts of saline were given equal to 3, 5, 7, 9, and 15 c.c. per 100 grams of body weight and survival tabulated.

Survival Following Plasma and Dextran Infusions With Untreated or Saline Controls.—This method allowed simultaneous comparisons of different therapeutic solutions and was thought to eliminate the hidden variables present in sequential testing (as opposed to simultaneous testing) techniques.

Simultaneous infusions of human plasma (Lyovac*) and normal saline in amounts equal to 3 and 5 c.c. per 100 grams of body weight were given and survival compared. Infusions of human plasma were then given in volumes equal to 2 and 1.5 c.c. per 100 grams of body weight and 48-hour survival noted. Untreated animals were used as controls for each group.

Simultaneous infusions of normal saline, 6 per cent dextran in normal saline† and 6 per cent dextran in 5 per cent glucose in water† were given in amounts equal to 5 and 7 c.c. per 100 grams of body weight. Untreated animals were used as controls.

RESULTS

Controls.—Varying time intervals of tourniquet application in untreated animals were used in the pilot studies. Tourniquet application for 3½ hours was found to be followed by a mortality rate of less than 20 per cent. Application of tourniquets for 4 hours produced an initial mortality in 6 to 8 animals and during further pilot experiments it was found that this 75 per cent ratio was continued in a larger group (21 of 28 rats). Following adoption of a 4½ hour trauma, there was a consistent mortality rate approaching 97 per cent (Table I).

The group of animals which was not subjected to the tourniquet trauma but which was subjected to the surgical manipulations followed by the infusion of normal saline showed no mortality.

Survival Following Graded Saline Infusion.—Table I lists both the daily and pooled results at the different levels of saline therapy except in the case of the control animals for which only the pooled data are shown. The reason for showing the data in this manner is to indicate clearly the degree of variation found from one working day to another in spite of rigid control of experimental conditions.

Table II shows the chi square analysis using pooled data comparing each replacement level against the control and against each of the other levels. It will be seen from this table that with the exception of the difference between 7 and 9 c.c. per 100 grams of body weight, all other differences are significant at the 5 per cent level or better.

*Merck Sharp & Dohme, Philadelphia, Pa.
†Abbott Laboratories, North Chicago, Ill.

TABLE II*

AMOUNT OF SALINE (C.C./100 GRAMS BODY WEIGHT)	3	5	7	9	15
0	$p < 0.01$	< 0.01	< 0.01	< 0.01	< 0.01
3		< 0.01	< 0.01	< 0.01	< 0.01
5			< 0.05	< 0.01	< 0.01
7				< 0.10	< 0.05
9					< 0.05

*Chi square evaluation of intravenous saline therapy comparing each replacement level against the control (0) and all other levels.

Survival Following Plasma and Dextran Infusions.—The results of simultaneous infusions with equal volumes of plasma and normal saline showed plasma to be more effective than saline at the 5 c.c. per 100 grams body weight replacement level, but not as strikingly so as at the 3 c.c. per 100 grams body weight level (Table III). The ratio of effectiveness of plasma to saline was thus shown to differ at each of two levels of replacement. This difference is significant as demonstrated by the use of a 2×4 chi square contingency table ($0.05 < p < 0.01$).

TABLE III*

VOLUME REPLACEMENT AS C.C./100 GM. BODY WEIGHT	PLASMA			SALINE			P VALUES
	LIVED	DIED	SURVIVAL (%)	LIVED	DIED	SURVIVAL (%)	
5	9	1	90.0	8	1	88.9	
	6	3	66.7	3	7	30.0	a vs b > 0.10
Pooled results	(a) 15	4	78.9	(b) 11	8	57.8	
3	8	2	80.0	1	9	10.0	
	9	1	90.0	1	8	11.1	c vs d < 0.01
Pooled results	(c) 17	3	85.0	(d) 2	17	10.5	
2	(e) 14	7	66.7				e vs f < 0.01
1.5	(f) 4	20	16.7				
0 (Control)	2	52	3.8	2	52	3.8	

*Forty-eight-hour survival in rats following treatment with continuous intravenous solutions of human plasma or normal saline (beginning 1 hour after tourniquet release and of 3 hours' duration) in otherwise lethal tourniquet trauma.

Because the survival rate of animals receiving saline at the 3 c.c. per 100 grams body weight level approached the control, separate infusions of plasma to all animals were performed using 2 c.c. per 100 grams and 1.5 c.c. per 100 grams body weight. Even allowing for daily variability in results, it may be seen that 2 c.c. per 100 grams body weight of plasma given in this experimental situation was protective to a highly significant degree (Table III).

The comparisons between saline and the two dextran preparations are shown in Table IV. With the dextran-glucose preparation, no protection was afforded since survival was 0 per cent. At both 5 and 7 c.c. per 100 grams

TABLE IV*

VOLUME REPLACEMENT AS C.C./100 GM. BODY WEIGHT	SALINE			DEXTRAN-GLUCOSE			DEXTRAN-SALINE			P VALUES
	LIVED	DIED	SURVIVAL %	LIVED	DIED	SURVIVAL %	LIVED	DIED	SURVIVAL %	
5	2	6	25.0	0	8	0	2	6	25.0	
	5	3	67.5	0	8	0	2	6	25.0	a vs b < 0.01
	6	2	75.0	0	6	0	5	3	67.5	b vs c < 0.01
										a vs c > 0.10
Pooled results	(a) 13	11	54.1	(b) 0	22	0	(c) 9	15	37.5	
7	4	3	57.1	0	7	0	1	6	14.2	
	8	0	100.0	0	8	0	5	3	67.5	d vs e < 0.01
	6	2	75.0	0	8	0	5	3	67.5	e vs f < 0.01
										d vs f < 0.05
Pooled results	(d) 18	5	78.3	(e) 0	23	0	(f) 11	12	47.8	
0 (Control)	2	52	3.8	2	52	3.8	2	52	3.8	

*Forty-eight-hour survival in rats following treatment with continuous intravenous solutions of saline, 6 per cent dextran in glucose solution and 6 per cent dextran in normal saline (beginning 1 hour after tourniquet release and of 3 hours' duration) in otherwise lethal tourniquet trauma.

body weight replacement levels, saline was apparently more effective than dextran in saline; however, this difference is not a statistically significant one (Table IV) in this study.

The data are graphically represented in Figs. 1 and 2.

Fig. 1.—Forty-eight-hour survival in rats following treatment with continuous intravenous solutions of human plasma or normal saline (beginning 1 hour after tourniquet release and of 3 hours' duration) in otherwise lethal tourniquet trauma.

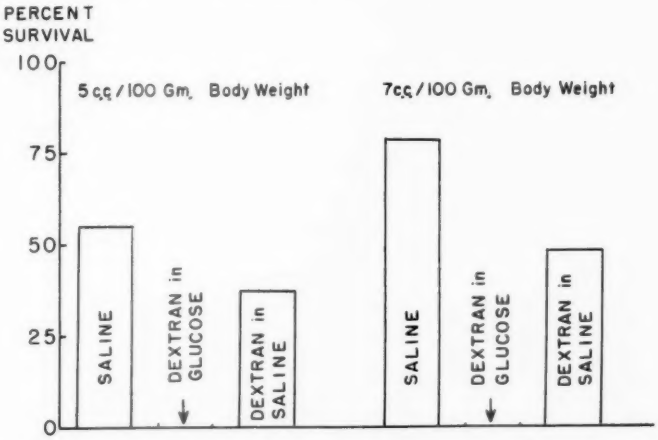

Fig. 2.—Forty-eight-hour survival in rats following treatment with continuous intravenous solutions of saline, 6 per cent dextran in glucose solution, and 6 per cent dextran in normal saline (beginning 1 hour after tourniquet release and of 3 hours' duration) in otherwise lethal tourniquet trauma.

DISCUSSION

Comparable data to that which is now being reported with saline administration have been presented by Koletsky's group[1] who also worked with the rat. Their infusion rate was more rapid and the infusion time varied with the volume replaced. Thus, it took about 22 minutes for their intravenous drip to deliver 6 c.c. per 100 grams of body weight, 60 minutes for 18 c.c., and 88 minutes to infuse 25 c.c. per 100 grams of body weight. In the present study, infusions were delivered over a constant time period, namely, 3 hours, or more than twice as long as their "slow" infusion. Fig. 3 compares the

Koletsky group's data with the present data. It would appear from this that the slower, more uniform saline infusions might be more efficacious in ameliorating the consequence of this shock procedure, although this is not necessarily the only explanation for higher survival with less fluid replacement currently observed.

Studies designed to test the comparative efficacies of different fluid therapy in the preparation used are fraught with difficulties. One difficulty stems from the number of animals that can be used for an experiment in a single day. Since this is a relatively small number and the measured end point of the determination is survival or death, the variable is not continuous. In dealing with a discontinuous variable and small numbers of animals, the death of an animal or two exerts a disproportionately large effect in the smaller groups. Thus, validity is to be found in large numbers. Further, since there is a sizable hidden variation inherent in the data (Table I), comparisons between treatment groups should be made simultaneously on the same experimental day rather than on different days. This observation has been previously made by Rosenthal and Tabor.[15]

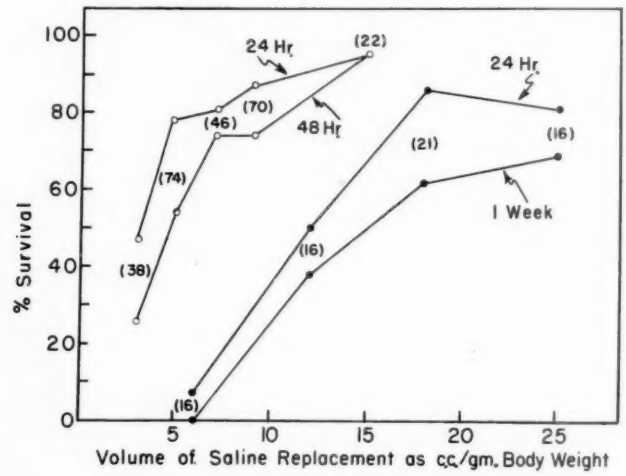

Fig. 3.—Per cent survival of rats subjected to tourniquet shock correlated with the method of saline infusion. The upper two curves represent the infusions used in these experiments while the lower two curves represent the method used by Koletsky's group.

It seems that a part of the observed daily variations stems not only from an inherent variability in the response of animals to treatment but also, to some extent, on the magnitude of the replacement therapy. At lower levels of fluid replacement the variation seems larger than at greater fluid replacement levels (see 3 and 5 c.c. per 100 grams body weight in Table I). This observation seems intuitively correct since the stability of the preparation progressively increases with increasing amounts of fluid replacement. This is demonstrated by comparing the better agreement between 24- and 48-hour survival data in groups receiving the larger replacements (Table I).

These findings would indicate that conditions have been established for the comparison of the efficacies of different fluid therapies, in spite of the inherent variation in repsonse to each such therapy in the tourniquet shocked

rat. These conditions include the slow administration of intravenous fluid over the period of greatest fluid loss in a controlled treatment situation, and the simultaneous comparison of different treatment groups.

Millican[9] has shown that equal volumes of saline and serum, given shortly after injury, produced essentially similar survivals when used to protect mice against an otherwise lethal tourniquet trauma. When treatment was delayed for 5 hours, a marked increase in effectiveness of serum therapy was observed, but no increased effect was observed from saline following late administration.

The same worker and co-investigators[10] have also found plasma therapy to be more effective in shocked animals when given in divided doses over a 7-hour period or when given intraperitoneally in a single dose. They attributed the increased effectiveness under these experimental conditions to decreased penetration of plasma protein into the edema fluid of the traumatized extremity with the passage of time and a diminished rate of accumulation of the therapeutic fluid in the traumatized extremity.

In the experiments here presented, plasma is again shown to be more effective than saline, the relative ratio of effectiveness of plasma and saline is shown to be different at different levels of therapeutic replacement. The explanation for this is not apparent. In addition, it is shown that small quantities of plasma (2 c.c. per 100 grams of body weight) may be highly effective in protecting against an otherwise lethal tourniquet trauma. In the present experiments, therapy was begun one hour after the release of tourniquets and fluid was administered over the period of greatest loss from the circulating volume.

The experiments in which 6 per cent dextran in normal saline and 6 per cent dextran in glucose in water are compared with saline for therapeutic effectiveness show saline to be the most effective of the three. The ratio of the effectiveness of saline to dextran in saline is about the same at replacement levels of both 5 and 7 c.c. per 100 grams of body weight. Any difference, however, between the two solutions is not statistically demonstrable with the numbers of animals utilized.

Dextran in glucose showed no therapeutic effect at all, mortality being 100 per cent with this agent.

It is understandable that plasma might be a more effective therapeutic agent in this type of trauma than saline alone because it has, in addition to its electrolyte elements, the colloidal properties of its protein. Both of these properties are important in adding and maintaining circulating volume. It is difficult to see, then, why a preparation of another colloid (dextran) in a normal saline solution should not show greater therapeutic benefit than the saline solution alone. However, on the basis of the observations using dextran in glucose in water, it seems unlikely that the colloidal properties of the dextran exert any beneficial effect in the treatment of this trauma. It is recognized that plasma is a buffered solution and that the saline solution used in these experiments is not buffered. Experiments are in progress to evaluate the relative therapeutic capacity of a buffered electrolyte solution compared to normal saline.

Cope and Moore[2] have shown that in trauma which alters the permeability of capillary membrane (thermal burn) colloid crossed the membrane at almost the same rate as electrolyte. Davis and co-workers[3] showed that whereas dextran in normal, dehydrated and bled animals re-expanded the plasma volume and maintained the re-expansion over a 4-hour period, in the face of altered capillary permeability (thermal burn), dextran was ineffective in maintaining adequate plasma volume expansion.

Finally, Rosenthal[14] and Moyer and his associates[13] have demonstrated that survival rates in burned animals treated with buffered electrolyte solutions equal or exceed the results of treatment with colloidal solutions.

Since tourniquet trauma does alter capillary permeability in the injured extremities, the results with the dextran solutions are explained, but the markedly superior effect of plasma is not thoroughly accounted for.

SUMMARY

A controlled treatment method for infusion therapy in tourniquet shock is presented. This method allows the slow administration of the therapeutic infusion over the period of greatest fluid loss from the circulating volume. Using this controlled treatment method, survival statistics have been obtained for intravenous saline infusions at 0 (control), 3, 5, 7, 9, and 15 c.c. per 100 grams of body weight. These survival statistics suggest that this slower, more uniform rate of saline infusion achieves higher survival rates at lower infusion volumes than have been previously reported in the rat. Because of the observed daily variation of results even in controlled experimental situations, simultaneous observation in adequate numbers must be made for accurate evaluation of experimental therapy.

Human plasma is shown to be a more effective therapeutic solution than normal saline in the treatment of an otherwise lethal tourniquet trauma in rats. The ratio of effectiveness of plasma to saline is shown to differ at each of two levels of replacement. Normal saline at the levels used is suggestively more effective than the 6 per cent dextran in saline preparation used in these experiments, but statistical significance is not shown. The 6 per cent dextran in glucose in water preparation used in the experiments showed no therapeutic effect in the treatment of tourniquet shock. The ineffectiveness of the plasma expander tested (dextran) in maintaining plasma volume expansion to any better degree than normal saline makes its use for the treatment of such trauma questionable.

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INTRA-AORTIC NITROGEN MUSTARD THERAPY IN ADVANCED PELVIC MALIGNANCIES

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THE treatment of advanced pelvic malignancies is a disheartening task and one that leaves much to be desired. During the last decade numerous chemotherapeutic agents have been used for either arresting or palliating neoplastic diseases. Few of these agents have had extensive clinical trial, while others are still in the investigative stage. None of these to date have been found to cure any neoplastic disease.

The treatment of a malignant tumor by injection of methyl-bis Beta-chloroethyl amine (HN_2) into its nutrient artery has been utilized as one point of direct attack.[6, 10] The regions best adapted to this form of therapy have been determined by the anatomy of their arterial blood supply and include extremities, brain, head, neck, and pelvis. Several investigations upon the blood supply of tumors have revealed that many neoplasms possess an increased arterial blood supply,[2, 9] increased capillary permeability,[5] and a characteristic vascular pattern upon arteriography.[7] These have also shown that administration of HN_2 intra-arterially results in higher concentrations of HN_2 at tumor site than can be attained safely by the intravenous route.[1] This knowledge has been applied to the treatment of mycosis fungoides lesions[4] of the extremities with prompt clearing of the involved areas and also to the therapy of many types of neoplasms unrelated to the lymphoid tissues. However, in no instance were the lesions completely eradicated. Klopp and associates[10, 11] treated superficially located carcinomas of the head and neck over 4 to 10 days with HN_2 intra-arterially and noted pronounced regression of the neoplasms. Krakoff and Sullivan[12] have reported on intra-arterial therapy of pelvic cancer via a polyethylene tube introduced through the femoral artery to the aorta above the bifurcation. Sixty-two per cent of their cases showed some degree of benefit.

A series of rabbits were treated with arterial nitrogen mustard associated with varying periods of venous occlusion. The rabbits were anesthetized, the femoral vessels were exposed surgically, and 2 mg. HN_2 was injected distally into the femoral artery. The rabbits were divided into four groups: (1) no femoral venous occlusion, (2) femoral venous occlusion for 5 minutes, (3) femoral venous occlusion for 10 minutes, and (4) femoral venous occlusion for 20 minutes.

Received for publication Aug. 18, 1958.

Group 1 tolerated the HN_2 without evidence of necrosis or functional abnormality. Group 2 showed small areas of necrosis over the anteromedial aspect of the upper thigh. The animals favored the leg when they walked. Group 3 showed extensive necrosis of the anteromedial aspect of the thigh—and the animals would not use the leg. Group 4 showed gangrene of the whole extremity. It was apparent from this experiment that venous occlusion increased the local effect of HN_2 delivered arterially in proportion to the time venous occlusion was maintained.

With this background in mind,[3] the present study was designed to investigate the effects of administering intra-aortic mustard therapy in advanced pelvic malignancies.

MATERIALS AND METHODS

The investigations were carried out by a team of surgeons, internists, anesthetists, and a radiologist. Thirty-four patients with advanced pelvic malignancies of various types comprise the material for this study (Table I). All diagnoses were confirmed by at least one relevant biopsy. Thirty of these 34 patients had been previously treated by definitive radiation therapy and/or surgery either elsewhere or in this hospital (Table II, *A* and *B*). The remaining 4 patients did not receive any previous therapy.

TABLE I. TYPES OF PELVIC MALIGNANCIES

TYPE	NUMBER
Vagina	1
Cervix	11
Uterine corpus	3
Ovary	9
Rectum and/or sigmoid	7
Anus	1
Kidney	1
Indeterminate	1
Total	34

Thirty-one patients were subjected to a pelvic laparotomy (Table II, *A*). After the usual manual exploration, the aorta, just above its bifurcation, and the inferior vena cava were exposed, and Penrose rubber drains were placed around them to serve as tourniquets. The arterial circulation in both lower extremities was occluded by special femoral artery pneumatic tourniquets. Following the occlusion of the femoral arterial circulation, a single injection of freshly prepared HN_2 in carefully regulated dosage was rapidly given into the aorta just above its bifurcation. During and following the injection, the aorta and the inferior vena cava were occluded above the injected site for 5 minutes. This allowed maximum arterial concentration of HN_2 in the tumor-bearing area of the pelvis. After the 5 minute period, all the tourniquets were released and the abdomen was closed. (Fig. 1.)

Three patients were treated by the arterial catheterization technique using the left brachial artery. With the patient under the routine preoperative medication and local procaine anesthesia, the left brachial artery was exposed and loops of thin rubber bands were placed around the vessel above and below

TABLE II. INTRA-AORTIC HN_2 THERAPY

PATIENT	SEX AND AGE	DIAGNOSIS	PREVIOUS THERAPY	HN_2 DOSAGE (MG./KG. BODY WEIGHT)	COMPLICATIONS	END RESULT REGRESSION OF TUMOR		SURVIVAL AFTER THERAPY (MONTHS)
						YES	NO	
			A. Exploratory Laparotomy					
E. W.	F 57	Carcinoma of cervix	Irradiation 14 years previously	*0.6	None	x		19
M. L.	F 48	Carcinoma of ovary	Subtotal hysterectomy and bilateral salpingo-oophorectomy followed by external irradiation 1 year previously	0.3	None		x	4
M. F.	F 63	Carcinoma of ovary	External irradiation therapy	0.4	None	x		7
J. B.	M 52	Carcinoma of rectum	Abdominoperineal resection 6 months previously	*0.6	None		x	6
A. C.	F 48	Carcinoma of cervix	Irradiation therapy 2 years previously	0.4	None		x	1
M. C.	F 51	Carcinoma of cervix	Radium therapy 2 years previously	0.4	None		x	11 Living
L. S.	F 53	Carcinoma of cervix	Irradiation therapy 12 years previously, radical hysterectomy 6 months previously	0.25	None	x		37
M. J.	M 51	Carcinoma of rectum	Abdominoperineal resection 1 year previously	0.3	None		x	7
G. B.	F 70	Carcinoma of vagina	Irradiation 8 years previously	0.3	None		x	6
M. B.	F 44	Carcinoma of cervix (stump)	Removal of cervical stump and irradiation 2 years previously	0.3	None		x	9
N. H.	F 70	Carcinoma of ovary	None	0.3	None		x	5
J. T.	M 38	Metastatic malignancy of unspecified origin	None	0.25	Died first postoperative day			
E. A.	F 50	Carcinoma of ovary	Surgery 4 months previously (details not known)	0.4	None		x	8 Living
I. B.	F 42	Sarcoma of uterus	Hysterectomy and bilateral salpingo-oophorectomy 2 months previously	0.35	None		x	30
L. G.	F 56	Carcinoma of ovary	None	0.35	Died second postoperative day			
L. R.	F 31	Carcinoma of cervix (stump)	Removal of cervical stump, pelvic lymphadenectomy and irradiation 6 months previously	0.3	None	x		24
L. W.	F 43	Carcinoma of ovary	Two courses of irradiation 6 months previously	0.4	None		x	5
A. N.	F 37	Carcinoma of cervix	Radium and hysterectomy 1 year previously	0.6	None		x	3
T. H.	F 59	Carcinoma of ovary	None	0.5	None		x	3
L. H.	M 63	Carcinoma of rectum	Abdominoperineal resection 4 years previously	0.55	None		x	4
A. R.	F 59	Carcinoma of rectum	Sigmoid resection 7 years previously, abdominoperineal resection and irradiation 5 years previously	*0.2	None	x		28
W. T.	M 56	Carcinoma of anus	Abdominoperineal resection 5 months previously	1.0	None		x	5
J. P.	M 67	Carcinoma of rectum	Exploratory laparotomy and colostomy for inoperable carcinoma 3 months previously	1.2	None		x	3

B. J.	F	20	Sarcoma of uterus	Hysterectomy, bilateral salpingo-oophorectomy, removal of large retroperitoneal pelvic tumor and sigmoid resection 5 months previously	1.3	Parotitis		x	2
B. G.	F	58	Adenoacanthoma of uterus	Treated with radium 26 years previously	0.95	None		x	5
M. B.	F	40	Carcinoma of cervix	Treated with irradiation 1 year previously	1.6	Died tenth post-operative day, shock (massive tumor necrosis)			
L. B.	F	26	Carcinoma of cervix	Treated with irradiation 8 months previously	1.3	None		x	6
R. D.	F	36	Carcinoma of cervix	Treated with surgery 10 months previously	1.2	None		x	4
J. B.	F	47	Carcinoma of ovary	Subtotal hysterectomy and bilateral salpingo-oophorectomy, followed by external radiation 3 months previously	0.8	None	x		Living 12
B. W.	F	52	Carcinoma of ovary	Bilateral salpingo-oophorectomy and external irradiation 2 years previously	0.9	None		x	Living 12
A. R.	F	51	Carcinoma of cervix	Irradiation therapy 3 years previously	0.8	None		x	4
				B. Brachial Artery Catheterization					
C. K.	F	45	Hypernephroma of kidney with metastases to femur and pelvis	Left nephrectomy and irradiation 4 years previously, HN_2 therapy arterially 2 years previously	0.8	None	x		7
L. H.	F	49	Carcinoma of recto-sigmoid	Low anterior colon resection 22 months previously, exploratory laparotomy and transverse colostomy 5 months previously	0.75	None		x	6
M. D.	F	63	Carcinoma of rectum	Abdominoperineal resection 5 months previously	0.67	None		x	Living 9

*These patients were given a second course of arterial therapy.

the site for the opening of the artery. A 2 mm. longitudinal incision was made through the wall of the artery with a small scalpel and the tip of the catheter was inserted. After insertion into the artery, the catheter tip was guided into the descending aorta by roentgenoscopy, to a point just above the aortic bifurcation. The catheter was left in place and the patient returned to the ward. Following occlusion of the femoral arterial circulation, HN_2 was injected through the catheter. The occlusion was maintained for 5 minutes following injection, and then released. In each instance the catheter was left in the artery 5 days without untoward effect.

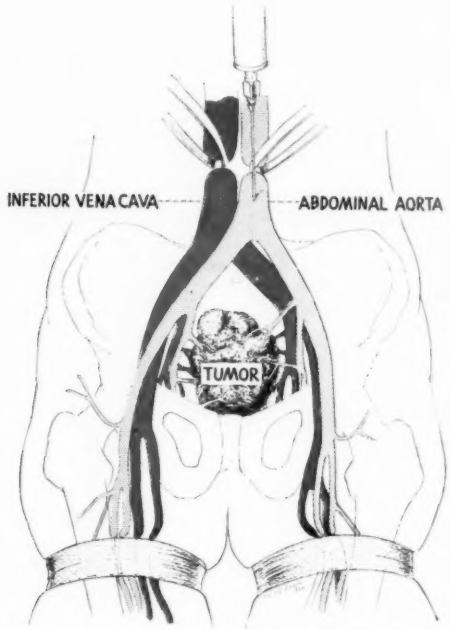

Fig. 1.—Intra-aortic injection with tourniquets in place.

DOSAGE

In the initial stages of therapy, comprising 21 patients, HN_2 ranging from 0.25 to 0.6 mg. per kilogram of body weight was administered. The remaining 10 patients were given a higher concentration of HN_2; the dosage ranged between 0.8 and 1.6 mg. per kilogram of body weight (Table II, *A*). (Fig. 2.)

The 3 patients treated by administering HN_2 through catheter received a total of 0.6 to 0.9 mg. per kilogram of body weight of the drug. (Table II, *B*).

RESULTS AND COMPLICATIONS

Twenty-One Patients Treated With Dosage of HN_2 Ranging Between 0.25 and 0.6 mg. per Kilogram of Body Weight (Table II, A).—Definite objective regression (measurement of palpable lesions) of tumor was noted in 5. One of these patients (LS) is still living 37 months after therapy. The other four (MF, EW, LR, and AR) survived 7, 19, 24, and 26 months, respectively. Of the 16 patients who did not show any objective evidence of regression of the tumor,

one (IB) is still living 30 months following therapy. The remainder survived for periods varying from 1 to 11 months. There were 2 postoperative deaths (JT and LG).

Ten Patients Treated With Dosage of HN_2 Ranging Between 0.8 and 1.6 mg. per Kilogram of Body Weight (Table II, A).—Only one of these patients (JB) showed objective evidence of regression of the tumor and is now living 12 months after therapy. There was one postoperative death (MB) from shock and bone marrow depression. On her ninth postoperative day, the WBC was 50. A marrow aspirate on this day showed a hypocellular marrow with an occasional particle. Erythropoiesis and megakaryopoiesis were absent. Leukopoiesis was markedly diminished at all stages. The few particles seen were comprised largely of elasmatocytes, plasma cells, and reticulum cells. The elasmatocytes contained hemosiderin granules. The plasma cells were both mature and immature. No myeloblasts or myelocytes were seen. Occasional P.M.N.'s and eosinophils were seen. Small lymphocytes were present and the differential count was as follows: 1 P.M.N., 1 P.M.E., 8 lymphocytes, 1 monocyte, 4 elasmatocytes, 4 plasma cells, 1 reticulum cell. The marrow was so hypocellular that only 20 cells were counted. The impression was a markedly hypocellular marrow following hematodepressant chemotherapy. Autopsy on MB revealed massive tumor necrosis in the pelvis. One patient (BJ) developed a postoperative parotitis which responded to irradiation therapy. She survived 2 months. Six patients lived for periods varying from 3 weeks to 5 months. One is still living 12 months after therapy.

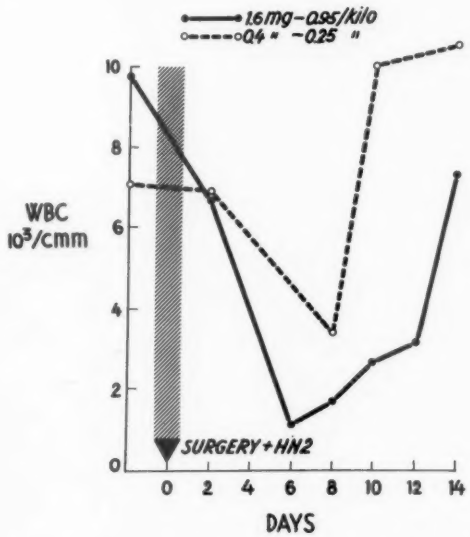

Fig. 2.—WBC depression. Large versus moderate dosage of HN_2.

Three Patients Treated With Dosage Ranging Between 0.6 and 0.9 mg. HN_2 per Kilogram of Body Weight Administered per Intra-arterial Catheter (Table II, B).—One of these patients (CK) who had repeated administration of the mustard survived 26 months and showed considerable subjective and objective improvement. One patient (LH) survived 6 months posttherapy with

considerable subjective relief of pelvic pain. The other patient (MD) is living 9 months posttherapy with considerable subjective relief of pelvic pain but no objective evidence of regression of the tumor. (Fig. 3.)

DISCUSSION

There is a growing feeling that surgery and irradiation alone or in combination cannot give the answer to the cancer problem, nor is there much hope that great improvements will be made in this therapy. Although chemotherapy will probably provide the ultimate solution for the control of cancer, there may well be a transitional period in which chemotherapy will be utilized to supplement the surgery and irradiation. The present study represents an attempt to combine the old and new modalities of treatment. The chemical, nitrogen mustard (HN_2), leaves much to be desired but was suitable for the study because of the widespread experience gained in its use, action, and long-range results over the past 12 years. Utilizing HN_2 via the arterial route enabled us to get a substantially higher dosage to the pelvis than by the usual intravenous route. This was further enhanced by applying arterial tourniquets to the legs.

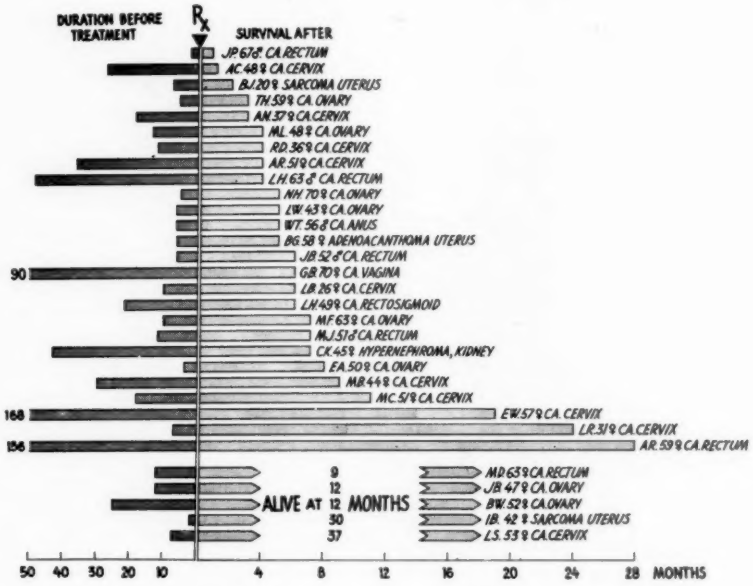

Fig. 3.—Influence of intra-aortic HN_2 on survival of patients with advanced pelvic malignancies.

The present study made full use of the known facts for enhancing regional chemotherapy. While the results are not too impressive with HN_2 this is largely due to limitation of the drug and not of the method. There is reason to hope that the basic principles utilized may be applicable as more effective chemicals become available.

SUMMARY AND CONCLUSIONS

Thirty-four patients with hopelessly incurable pelvic malignancies were treated with intra-aortic HN_2 in doses ranging from 0.2 to 1.6 mg. per kilogram

of body weight. Of these, 31 were subjected to an exploratory laparotomy and intra-aortic administration of the drug with venous occlusion at the time of surgery. The remaining 3 patients were treated by administration of the drug through an indwelling intra-aortic catheter.

2. Seven cases showed objective improvement.

3. There were 3 postoperative deaths in this series.

4. The results and implications of HN_2 therapy are discussed.

5. In our hands, arterial HN_2 therapy has proved to be of some significance in the palliation of advanced pelvic malignant diseases.

6. Patients who have malignant tumors localized to the pelvis which are not amenable to surgery or irradiation are suitable for intra-aortic nitrogen mustard therapy. This is particularly true when the tumor has involved the lateral pelvic walls. The final decision to utilize chemotherapy frequently must be made at the operating table during the exploratory laparotomy. HN_2 can be administered safely via the aorta in doses of 0.25 to 1.3 mg. per kilogram.

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ENHANCEMENT OF METHYLCHOLANTHRENE CARCINOGENESIS BY DISTANT SURGICAL TRAUMA

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TRAUMA has been reported to accelerate the rate of occurrence of skin carcinoma in animals painted with methylcholanthrene. Such trauma usually has been locally applied to the areas painted with the carcinogen.

Incisions made in the skin of tarred mice[4] caused tumors to appear with unusual rapidity. The skin of rabbit ears was painted until a few benign growths appeared and the paintings were then stopped. Punch holes made later in the previously treated skin areas resulted in the appearance of tumors.[5] Cauterization to the base of a skin wart in the induction phase predisposes to accelerated malignant changes.[2] Excisional biopsy enhances the rate of occurrence of epidermal tumors.[7] Nonsurgical irritants such as heat or croton resins can influence the conversion of benign epithelial tumors into cancers.[1]

We are reporting the enhancement of distant surgical trauma to unpainted skin and its accelerating effect on the appearance of skin carcinomas appearing in areas painted with methylcholanthrene.

METHOD

A 0.6 per cent solution of 20-methylcholanthrene in a reagent grade of benzene was applied to the dorsal unepilated interscapular skin of DBA/1 mice with a No. 4 camel's-hair brush. A single stroke delivered about 0.1 mg. of methylcholanthrene.[3] Paintings were done on 100 DBA/1 mice 3 times weekly for 3, 6, 9, and 12 weeks. Observation period of these painted mice was 10 months after the completion of skin painting. Animals were done in groups of 10 and the experiments were repeated 2 or 3 times. The 9 weeks of dorsal skin paintings resulted in the appearance of squamous cell carcinomas in all of the 20 animals. This time and dosage of painting seemed to be critical to the incidence of induced carcinomas as compared to the groups painted every 3 and 6 weeks (Table I).

An additional experiment was then planned to determine any effect of distant trauma on the enhancement of methylcholanthrene carcinogenesis. A total of 60 DBA/1 mice were painted with methylcholanthrene 3 times weekly for 3 and 6 weeks. After the skin paintings were completed, surgical trauma was done immediately, and at periods of 1 or 2 months (Table II). Trauma consisted of a one-centimeter surgical incision through the full thickness of the

Supported by Grant No. VI-18 of the American Cancer Society.
Received for publication Oct. 24, 1958.

midline belly skin. The incision was then resutured with 4-0 black silk. This group of traumatized animals was also observed for 10 months after the completion of skin painting.

TABLE I. INCIDENCE OF SQUAMOUS CELL INDUCED METHYLCHOLANTHRENE CARCINOMAS IN DBA/1 MICE

DURATION OF DORSAL SKIN PAINTING* (WEEKS)	NUMBER OF ANIMALS DEVELOPING TUMORS	APPEARANCE OF SKIN CANCER (MONTHS)
3	1/30	5
6	3/30	3
9	20/20	2-3
12	20/20	2-3

Observation time, 10 months.
*Three times weekly.

TABLE II. ENHANCEMENT OF INDUCED METHYLCHOLANTHRENE CARCINOGENESIS IN DBA/1 MICE BY TRAUMA

DURATION OF SKIN PAINTING* (WEEKS)	TIME SURGICAL TRAUMA DONE AFTER COMPLETION OF SKIN PAINTING AND INCIDENCE OF TUMORS				
	IMMED.	1 MO.	2 MO.	TOTAL NO. OF TUMORS	APPEARANCE OF SKIN CANCER
3	1/10	4/10	0/10	5/30	6 to 9 months
6	7/10	7/10	7/10	21/30	6 to 9 months

Observation time, 10 months.
*Three times weekly.

RESULTS

The incidence of squamous cell carcinomas, resulting from skin paintings 3 times weekly for 3, 6, 9, and 12 weeks, are reported in Table I. The accumulative dosage of methylcholanthrene at the 9-week painting was effective in producing squamous cell carcinomas in all of the 20 animals. The 12-week skin paintings also produced tumors in all of the animals. The 3- and 6-week paintings showed a low incidence of skin tumors and reflect the factors of time and dosage in the production of methylcholanthrene carcinogenesis.

The effect of distant trauma on the enhancement of induced methylcholanthrene carcinogenesis in DBA/1 mice is shown in Table II. The 3-week painted animals, when traumatized, showed a total tumor incidence of 5 of 30 animals as compared to an incidence of 1 of 30 in the nontraumatized group. The 6-week painted traumatized group showed a total tumor incidence of 21 of 30 animals as compared with 3 of 30 in the nontraumatized group. The time of surgical trauma after the completion of skin paintings did not seem to influence the enhancement of tumor formation.

DISCUSSION

We have reported the observations of induced lymphosarcoma resulting from the transplantation of skin grafts from animals treated with methylcholanthrene. Squamous cell carcinomas were induced on the dorsal interscapular skin of DBA/1 mice after daily paintings for 9 weeks. Four months after the squamous cell cancer appeared in the painted dorsal skin area, full thickness

skin grafts were taken from the grossly normal-appearing ventral surface and transplanted to untreated DBA/1 mice. Twenty-one days after transplantation, 6 of 10 mice died of lymphosarcoma.[6] These observations made us wonder about the systemic effects of distant surgical trauma when added to induced carcinogenesis.

The enhancement of local trauma to the same areas of skin exposed to carcinogen could be explained by the additive effects of irritation. It has been postulated that an applied irritant induces a continued state of reparative hyperplasia which is different and distinct from ordinary process of repair. These classical phases are induction where hyperplasia is predominant, benign tumor formation, and cancer.

Regenerated epithelium, rendered abnormal by a carcinogen, can have its malignant process hastened by noncarcinogenic irritants such as local surgical trauma.

One has to consider other mechanisms of tumor acceleration when surgical trauma is produced at a distant site, as in our experiments. One hypothesis immediately presenting itself is a stress reaction mediated via hypothalmic pituitary adrenal mechanism.

Hypophysectomy has been reported as inhibiting methylcholanthrene carcinogenesis.[8] It is also well known that hypophysectomy causes adrenal cortical atrophy and inhibits stress response. Conversely, it is possible that the stress of surgical trauma could produce an enhancement of tumor appearance and growth through pituitary adrenal effect.

SUMMARY

Surgical incisional trauma to distant untreated skin potentiates induced carcinogenesis in the skin areas painted with methylcholanthrene in DBA/1 mice. The theoretical role of such enhancement is presented.

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MECHANICAL FAILURE DURING EXTRACORPOREAL CIRCULATION

A Method for Prevention

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INTRODUCTION

SINCE 1952, the use of mechanical devices to support the circulation has become widespread. For varying lengths of time during extracorporeal circulation, the patient's life is dependent upon the reliability of the pumping device. That sudden mechanical failure without warning can occur was recently tragically demonstrated.

CASE REPORT

This was the seventh Mount Sinai Hospital admission of a 46-year-old white woman with known mitral insufficiency of a severe degree. This patient had been in intractable heart failure.

On March 11, through a right thoracotomy an attempt was made to repair the mitral insufficiency. The bubble oxygenator and Sigmamotor pump (model TM2) were used.[1] The femoral artery catheter was inserted, the vena cavae was cannulated, and the pump was turned on. Upon opening the left atrium a markedly dilated annulus was observed. After 20 minutes of perfusion the repair of the annulus was almost complete. Until then the perfusion had proceeded without incident at flow rates between 4,000 and 5,000 c.c. per minute. Abrupt cessation of pumping activity then occurred. This was associated with immediate disappearance of blood pressure and electroencephalographic activity. The large atrial incision was partially closed quickly, a clamp was applied to the remaining opening, the caval catheters were removed, and attempts were made to restore circulation. There was a period of approximately 3 minutes during which there was no blood pressure or electroencephalographic activity. Despite long massage, epinepherine, calcium chloride, and other measures, an effective heartbeat could not be restored.

There is no doubt that this patient had a diseased myocardium as well as valvular lesions, nevertheless the fact that an adequate repair had been done leads one to believe that she would have had a good result.

DISCUSSION

There have been approximately 2,200 cases of cardiopulmonary bypass performed in this country. The Sigmamotor pump has been utilized in about 1,700 of these cases.[2] The newer pump, TM2, although essentially the same, is more compact, produces less noise, and has a greater output. This is the first reported clinical failure of a Sigmamotor pump. We know of one other clinical failure

Supported in part by Grant HTS-5206, the National Heart Institute, U. S. Public Health Service.

Received for publication Sept. 23, 1958.

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in which the TM1 was used.[3] Undoubtedly laboratory failures have also occurred. Although Sigmamotor equipment was used in this instance, mechanical failure is possible with any type of pumping device.

The cause of failure in our case was the abrupt disruption of the coupling between the motor and gear box.

The following factors are important in preventing a mechanical failure during perfusion: (1) adequate fusing, (2) lock plugs, (3) frequent check of oil levels in motor, gear box, and pump heads, (4) avoidance of overloading the torque capacity (the Vernier dials should not be pushed past the maximum setting), and (5) careful investigation by a factory representative of overheating or any unusual noises emanating from the gear box or pump heads.

Despite all the above precautions, acute mechanical failure can still occur. To prevent this, two Sigmamotor pumps can be placed in parallel with Y connectors. Then failure of one device can be immediately compensated for.

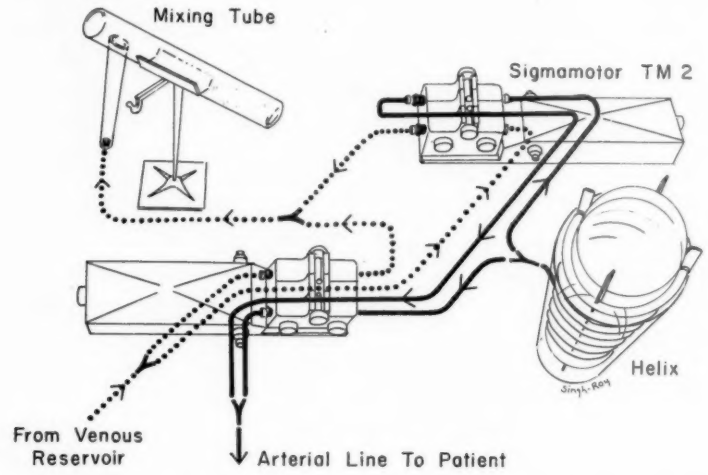

Fig. 1.—Diagram of Y connectors for parallel arrangement of Sigmamotor pumps model TM2. Dotted lines (. . .) indicate venous side of pump. Black lines indicate arterial side of pump. Arrows indicate direction of blood flow. There is latex tubing in the pump head. The Y connectors are ⅜ by ⅜ by ⅜ inch.

The arterial side of the nonfunctioning pump is primed before the perfusion and the Verniers adjusted for an adequate flow rate. Because the pumps are occlusive, with inflow and outflow Y connectors, it is now possible to maintain perfusion with either pump merely by turning a switch. Fig. 1 illustrates the arrangement of the pumps and connectors. This method is simple and requires only another 100 c.c. of blood for priming.

CONCLUSIONS

1. During cardiopulmonary bypass, the patient's life depends upon the reliability of the mechanical pumping device.

2. Despite all precautions, mechanical failure may still occur without warning. A case report of such an occurrence is presented.

3. To prevent sudden failure, it is recommended that two pumps be used in parallel with inflow and outflow Y connectors, thus allowing immediate change-over.

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ETHYLENE OXIDE STERILIZATION OF A COMPLETELY ASSEMBLED VERTICAL SCREEN PUMP-OXYGENATOR

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THE use of plastic materials wherever blood contacts the surfaces of extracorporeal apparatus seems important and it is obviously desirable that containers and tubing be transparent. As far as we know, there are no transparent plastics available at present which will repeatedly withstand steam sterilization. For cold sterilization, the assembled apparatus has been filled with Zephiran[8] or formaldehyde[1, 2] and then flushed with copious amounts of sterile saline solution. Uncertainty about the reliability of these sterilizing solutions has led to a continuing search for other agents. Warexin,† which was recently introduced, is undergoing clinical evaluation.[20]

Extracorporeal apparatus has also been sterilized by soaking the dissembled parts in a 13 per cent weight solution of formaldehyde. The parts are then rinsed with sterile water, dried, and assembled aseptically. This process was used by us in more than 25 patients without evidence of infection or untoward reactions. There is no doubt, however, that the procedure is unpleasant, technically difficult, and time-consuming. We have, therefore, turned to still another form of cold sterilization—the use of a bactericidal gas (ethylene oxide).

During World War II, Dr. Charles R. Phillips,[19] of the Department of Biological Warfare at Fort Detrick, was asked to devise a method of sterilizing any article which might be contaminated if biological warfare were employed. He and his associates soon became convinced that the only practicable method was the use of a bactericidal gas. Subsequently, ethylene oxide gas was found to fulfill most of the requirements. It had previously been used for industrial fumigation and sterilization for over 15 years.

The major disadvantages of ethylene oxide were its extreme explosiveness and inflammability in high concentrations. It is a cyclic ether with a

Supported by U. S. P. H. S. Grant 2331-C, The John A. Hartford Foundation, Inc., and the York County Pennsylvania Heart Association.
Received for publication Sept. 29, 1958.
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very unstable chemical structure. These undesirable aspects have been modified by admixture with inert gases. A 10 per cent weight ethylene oxide and 90 per cent carbon dioxide mixture (Carboxide*) has been available for many years. Recently an 11 per cent weight ethylene oxide and 89 per cent inert gas mixture (Cryoxide†) and a 12 per cent ethylene oxide and 88 per cent inert gas mixture (Steroxide‡) have become available. These mixtures are not explosive or inflammable when released in room air.[6, 15, 16]

While Carboxide is somewhat cheaper than the other two gas mixtures, it has certain disadvantages:

1. Carboxide is provided in 30 and 60 pound steel cylinders, and at least 20 per cent by weight of the contents of each cylinder must be used each time to be certain that the gas emitted will be in the stated concentration.[3] Also, it has been reported that the effectiveness is decreased after one-half of the gas in each cylinder has been used.[14] On the other hand, Cryoxide can be obtained in 21 ounce weight cans and Steroxide in 22 and 36 ounce weight cans. Even smaller amounts can be obtained in "Steribulbs."[12] The cans require special opening valves which can be obtained from the respective manufacturers.§ These valves are not interchangeable.

2. Three times more Cryoxide or Steroxide can be put into a given container under the same pressure, temperature, and volume conditions. This is because the inert gas (a member of the dichlorodifluoromethane group) has a molecular weight approximately three times that of carbon dioxide.

TOXICITY

The gas is readily detected by its odor, which is similar to that of ether. In low concentrations, the first symptoms of heavy exposure are due to irritation of the mucous membranes and resemble those caused by ammonia. These are followed by nausea, vomiting, and dizziness. Thus, there is ample warning.[7, 21]

Liquid ethylene oxide may cause contact dermatitis on prolonged exposure, by contact, with saturated clothing, rubber gloves, shoes, etc. When falling directly on the skin, however, Steroxide and Cryoxide vaporize rapidly and cause little harm.[22, 23]

STERILIZING PROPERTIES

Phillips[11, 17, 18] tested the sterilizing properties of ethylene oxide against various pathogenic bacteria and *Bacillus globigii* spores *(B. subtilis* var. *niger)*. These spores are not pathogenic and they form large orange colonies. They are even more resistant than pathogens and are, therefore, used as test organisms. Other investigators have performed extensive studies of the sterilizing properties of ethylene oxide and all have confirmed the observations of Phillips.[4, 5, 10, 13, 26]

*Union Carbide and Carbon Co., 30 E. 42nd St., New York, N. Y.
†American Sterilizer Co., Erie, Pa.
‡Wilmot Castle Co., Rochester, N. Y.
§Valves for Cryoxide can also be obtained from the Superior Valve and Fittings Company, Pittsburgh, Pa. (Dual Charging Can Valve 224BX2).

The time required for sterilization depends on five variables: the concentration of the ethylene oxide, the temperature, the humidity, the physical characteristics of the object being sterilized, and the organisms present.[9] Fig. 1 is a plot of Phillips' original data for *B. globigii* spores, which were placed on filter papers and hung in vessels where the concentration of ethylene oxide, the humidity, and other factors could be varied. While useful, these curves should be used only as a rough guide. Excellent descriptions of minimum operating conditions are obtainable from manufacturers interested in this field.*

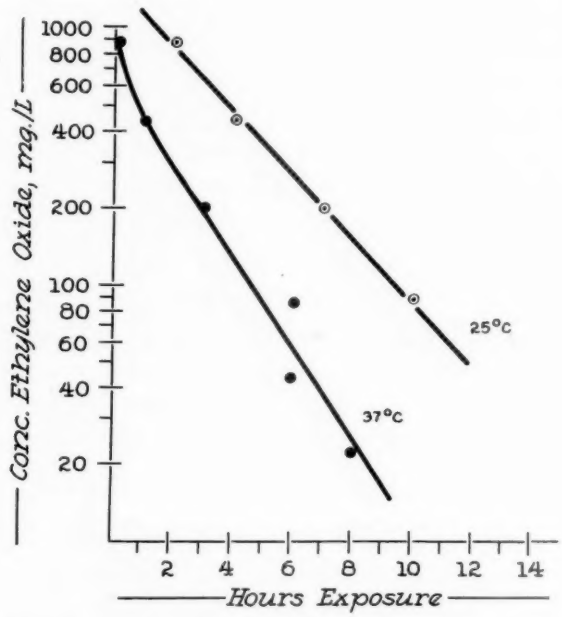

Fig. 1.—Exposure time required to kill all *B. globigii* spores. (Data from Phillips.[37])

EQUIPMENT

Small commercial gas sterilizers are available but they are rather expensive and the cost of large sizes may limit their use. A regular steam sterilizer can be altered for gas sterilization at a cost of less than $200.00. This type of unit has been used by the Extracorporeal Circulation Unit at Johns Hopkins Hospital for over one year.[24] A commercial pressure cooker can easily be converted and any container which will hold the gas can potentially be used.

At the Hospital of the University of Pennsylvania we are using a 61 cubic foot chamber made of No. 304 stainless steel with walls ⅛ inch thick (Fig. 2). It was built to withstand an internal pressure of 5 p.s.i.g. (pounds per square inch gauge) and is equipped with an overpressure safety valve. Provision has been made to exhaust the gas mixture and circulate filtered air, after an adequate exposure period, at a rate of 50 cubic feet per minute. Since humidity is an important variable only when very high or very low,

*American Sterilizer Co., Erie, Pa., and Wilmot Castle Co., Rochester, N. Y.

no attempt is made to alter ambient humidity. This is permissible because a vacuum is not used at the beginning of the sterilization cycle. Sterilization takes place at room temperature which varies between 25° C. and 30° C. We have sacrificed rigidity in controlling factors which would shorten the time required for sterilization in favor of simplicity of operation.

PROCEDURE

After the individual parts have been washed and dried, the apparatus is assembled and the entire pump-oxygenator is rolled into the sterilizing chamber. Care is taken to see that none of the tubing is kinked or obstructed, and the tubing is not wired to the connectors. The chamber door and the exhaust and air inlet valves are closed. Gas is then admitted to the chamber until the internal pressure reaches 5 p.s.i.g. This requires five 21 ounce cans of Cryoxide, which provide a concentration of approximately 200 mg. of ethylene oxide per liter of gas.

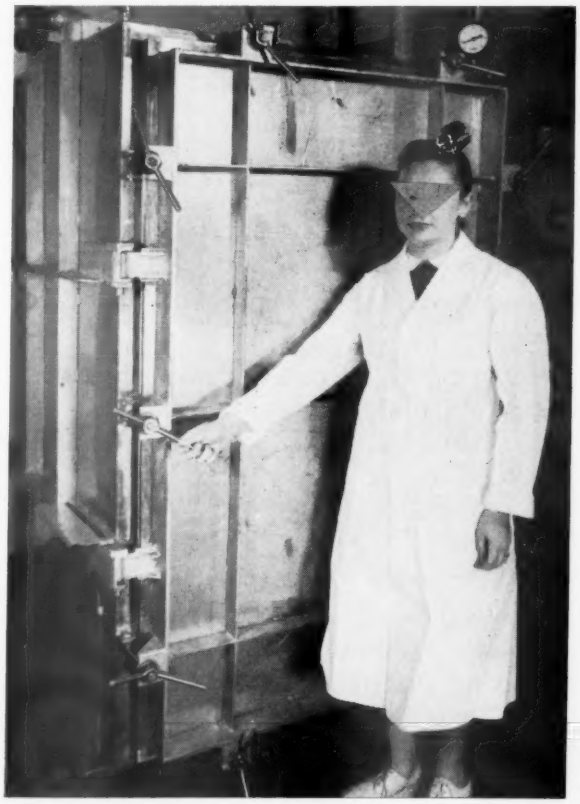

Fig. 2.—Sixty-one cubic foot ethylene oxide sterilizing chamber, shown with laboratory technician opening the door.

The sterilizing mixture is in liquid form in the can, and it vaporizes on entering the chamber. To prevent the subsequent cooling of the walls of the chamber, external heating elements have been attached where the ethylene oxide vaporizes. These are turned on briefly before the sterilizing gas is introduced and they are thermostatically controlled to maintain a local wall

temperature of 40° C. When the pressure has reached 5 p.s.i.g., the heaters are turned off (usually after about 15 minutes). The sterilization then takes place at room temperature (25° to 30° C.).

Reference to the curve in Fig. 1 shows that these conditions should, theoretically, provide sterilization in 7 hours. However, these test organisms were not shielded in any manner, and it requires longer for the gas to disseminate through semiclosed apparatus. This is especially true of thick-walled tubing, since the gas must circulate down through its lumen.[25] This is a handicap imposed by not using a vacuum at the beginning of the sterilizing cycle.

After exposure of our completely assembled vertical screen pump-oxygenator* for 12 hours, we have found no growth of *B. globigii* spores placed at various locations, including those most inaccessible to the gas. Samples taken from the patient tubes, which are 6 feet long, have been positive, however. These tubes should be autoclaved, and attached after the oxygenator has been removed from the sterilizer.

At present, the apparatus is exposed to the gas in the sterilizing chamber for a minimum of 16 hours. It is left in the chamber overnight, and on the morning of operation the gas is exhausted to the atmosphere and air is circulated through the chamber for one hour. This air enters through a filter and leaves via the exhaust line.

The apparatus is then removed from the chamber, the arterial, venous, and coronary suction lines are attached, and all connections are wired. The control boxes are connected and the apparatus is rolled to the operating room—ready for use.

When not in use, the apparatus can be stored in the chamber and is ready for use any time after 16 hours of exposure to the gas. Exposure for as long as 48 hours has not adversely affected either the apparatus or the patient in any manner that we can detect.

DISCUSSION

By using the ethylene oxide gas chamber constructed for us† our entire vertical screen pump-oxygenator can be assembled and sterilized as a complete unit. If previously wrapped with drapes, it can then be transported anywhere. The sterilizing chamber should, ideally, be large enough to house the entire apparatus. In attempting to hold down the cost of a large unit, we have accepted the longer exposure period necessary without the costly provisions required for safe temperature elevation and relatively great pressure changes. Our 61 cubic foot stainless steel chamber cost less than $1,500.00, in contrast to the present price of approximately $5,000.00 for a 4 cubic foot commercial gas sterilizer.

An additional advantage of a large chamber is that other large objects, such as mattresses, can be sterilized. Also, larger loads of smaller articles,

*Mark Company, Randolph, Mass.
†Perry Products Manufacturing Company, Philadelphia, Pa.

such as anesthesia masks and tubing, can be accommodated at one time, when the time factor is not critical.

In using ethylene oxide successfully, it is essential to know that the articles to be sterilized must be clean and dry. The gas will not penetrate dried layers of debris and it diffuses slowly into liquids. Also, when a vacuum is not used, time must be allowed for the ethylene oxide to diffuse into the lumen of tubing, into containers, etc. When a vacuum is used at the beginning of the cycle, water vapor must be introduced into the sterilizing chamber along with the ethylene oxide. Otherwise, the humidity in the chamber will be low and this reduces the bactericidal activity.

Before using such a sterilizer, it is important to carry out the bacteriologic studies which are needed to confirm the effectiveness of this method for the articles to be sterilized.

We have recently received reports from other hospitals that ethylene oxide has apparently caused Lucite parts to "flake" and become opaque. This followed the use of both the commercial and the converted steam type sterilizers. It seems not unlikely that the direct contact of liquid ethylene oxide or inert compound was responsible, either by causing a chemical reaction or severe local chilling of the Lucite during vaporization. We have used special precautions to prevent direct contact of the liquid with the plastic and have not observed this reaction.

SUMMARY

Ethylene oxide gas has been used to sterilize a completely assembled vertical screen pump-oxygenator, many parts of which cannot be heat sterilized. Special provisions required for the relatively wide fluctuations of temperature, pressure, and humidity needed to shorten the sterilization cycle were omitted in favor of economy and simplicity of operation. Completely reliable sterilization was produced by exposure to ethylene oxide in a concentration of 200 mg. per liter for 16 hours at room temperature and ambient humidity. An outstanding advantage of this method is that the pump-oxygenator is assembled and ready for use when it is wheeled out of the sterilizing chamber.

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THE DEVELOPMENT OF ATHEROMA IN ARTERIES SUBJECTED TO EXPERIMENTAL THROMBOENDARTERECTOMY

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THE fate of the arterial wall after thromboendarterectomy has been under study in our laboratory. After intima and a portion of media are removed from a canine aorta, the denuded area is covered by a thin thrombus which gradually organizes and forms a firm collagenous layer (Fig. 1), the surface of which resembles normal intima.[4, 8] In 18 animals in which this procedure was carried out, no evidence of spontaneous atherosclerosis was seen after 1 to 6 months of normal diet. Atherosclerosis is occasionally seen spontaneously only in elderly dogs. From the observations of Duguid,[2, 3] one is led to believe that human atherosclerosis is a result of mural thrombi which, after becoming covered with intima, develop into subintimal atheroma. It is also a well-documented observation that any trauma to a blood vessel in the presence of proper dietary lipemia is an important factor in experimental atherosclerosis. It was felt that the experimental endarterectomy could serve as a useful tool for observing the fate of the regenerating arterial wall in the presence of hypercholesterolemia and, second, to test Duguid's theory.

METHODS

Ten adult mongrel dogs were subjected to resection of the aortic intima through an open aortotomy. The aorta was closed, and in periods ranging from 1 to 120 days postoperatively the animals were placed on a diet of pure cholesterol (5 per cent of the total intake) and oral propylthiouracil† (0.5 Gm. daily), after the method of Steiner and associates.[6, 7] Serum cholesterol determinations were made at monthly intervals as a guide to therapy. These were done by the method of Schoenheimer and Sperry.[5] All of the animals were sacrificed at between 5 and 6 months by using an overdose of intravenous Nembutal. No anticoagulants or antibiotics were used at this time. At time of sacrifice, the heart, the entire aorta, and the iliac and femoral vessels to the groin were excised. The aorta and its branches were opened longitudinally and carefully examined for evidence of atheroma. After this, the specimens were placed in formalin (10 per cent) and were stained with

This work was aided in part by a grant from the Berkshire County Chapter of the Massachusetts Heart Association, and also by a research grant, H-3345, from the National Heart Institute, U. S. Public Health Service.

Received for publication Oct. 22, 1958.

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†Supplied by Eli Lilly & Company (Lilly Laboratory for Clinical Research).

hematoxylin and eosin, Weigert's elastic tissue stain, and Sudan black by frozen section. The degree of atheroma was graded from 1+ to 4+, in which 1+ indicated barely visible pinpoint lesions and 4+ multiple coalescent lesions.

RESULTS

The degree of hypercholesterolemia was only moderate, ranging from two to five times above the normal prediet level.

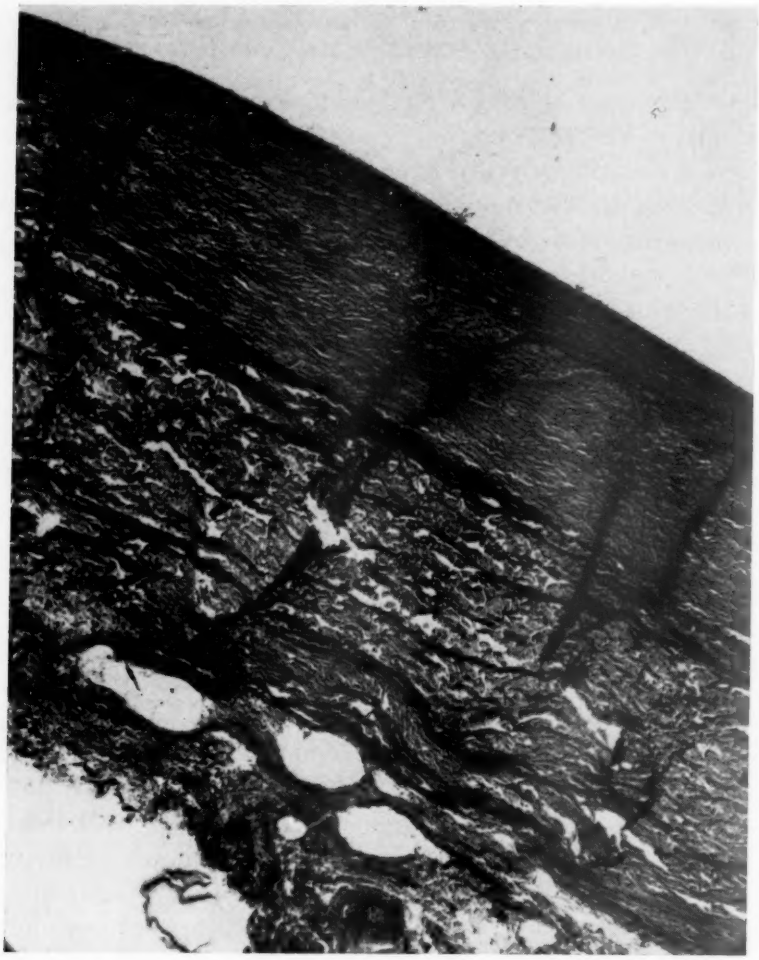

Fig. 1.—Microscopic appearance of canine aorta 2 months after intimal resection showing newly formed collagen layer (*top*). This animal did not receive cholesterol or propylthiouracil. (Verhoeff-van Gieson stain. ×20; ⅕ off reduction.)

In all of the animals sacrificed, the area of intimal resection was patent with no evidence of constriction. One specimen demonstrated an area of roughened intimal surface resembling minor stalactites, but the remaining specimens were all quite smooth, glistening, and translucent, so that the silk sutures could readily be seen through the newly formed intimal surface. All of the specimens showed a relatively normal aorta, except for the segment of regenerated endothelial surface. In all of the animals in the area of the

regenerated endothelial surface, there were areas which showed varying degrees of distinct atheroma grossly. These appeared as rounded or irregular streaked areas, often raised, yellow-orange plaques ranging in size from 0.1 to 2 cm. in greatest dimensions (Figs. 2 and 3). Microscopically, these areas stained heavily with Sudan black and appeared to be only in the newly formed collagen layer. These appeared as well-localized deposits of lipid (Fig. 4) and in other areas they showed up as a diffuse lipoid deposition throughout the newly formed collagen layer (Fig. 5). With this relatively low level of hypercholesterolemia, none of the other major arterial trunks examined, including the coronary, the aorta, intercostal, lumbar, iliac, and femoral arteries showed any evidence, grossly or microscopically, of atheroma formation or sudanophilia.

Fig. 2.

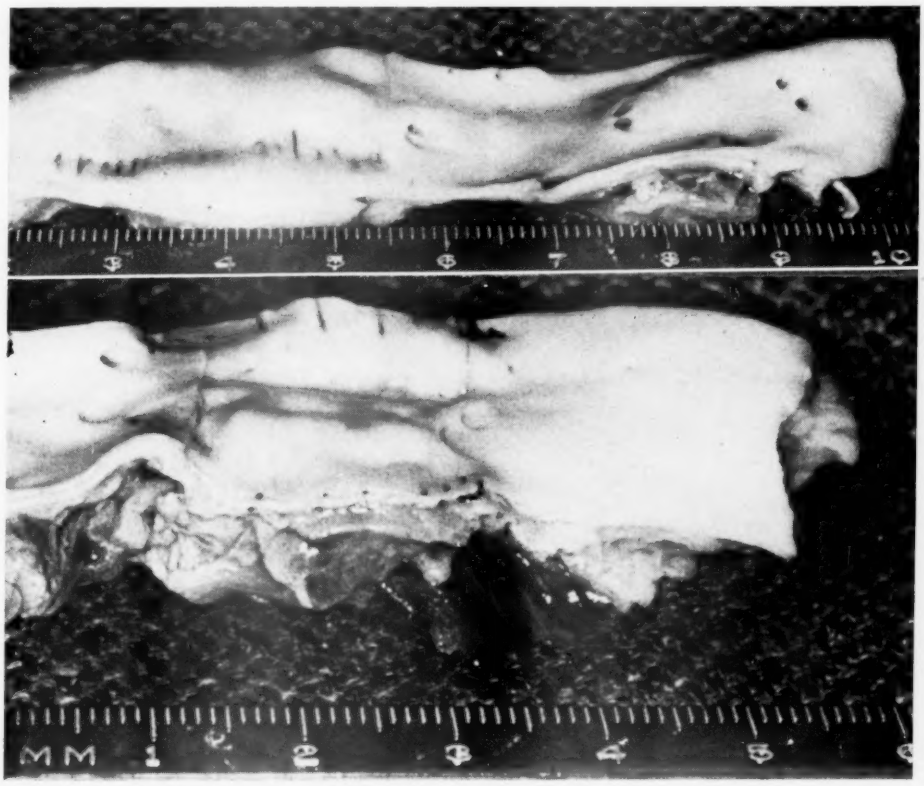

Fig. 3.

Fig. 2.—Photograph of canine aorta 6 months after intimal resection. Cholestrol and propylthiouracil were not given. Note the smooth appearance of newly formed "intimal layer" marked by silk sutures used to close aortotomy.

Fig. 3.—Photograph of canine aorta 6 months after intimal resection and 5½ months of cholesterol and propylthiouracil administration. There is plaque formation and streaking in the segment of newly formed "intima."

From Table I, it appears that there is *not* a distinct relationship between the mean cholesterol level and degree of atheromatosis. In Dogs 7 and 129, relatively high levels of serum cholesterol were maintained with only minor degrees of atheroma formation, whereas Dogs 18 and 30 showed distinct atheroma with mean serum cholesterol levels below 200 mg. per cent.

Fig. 4.

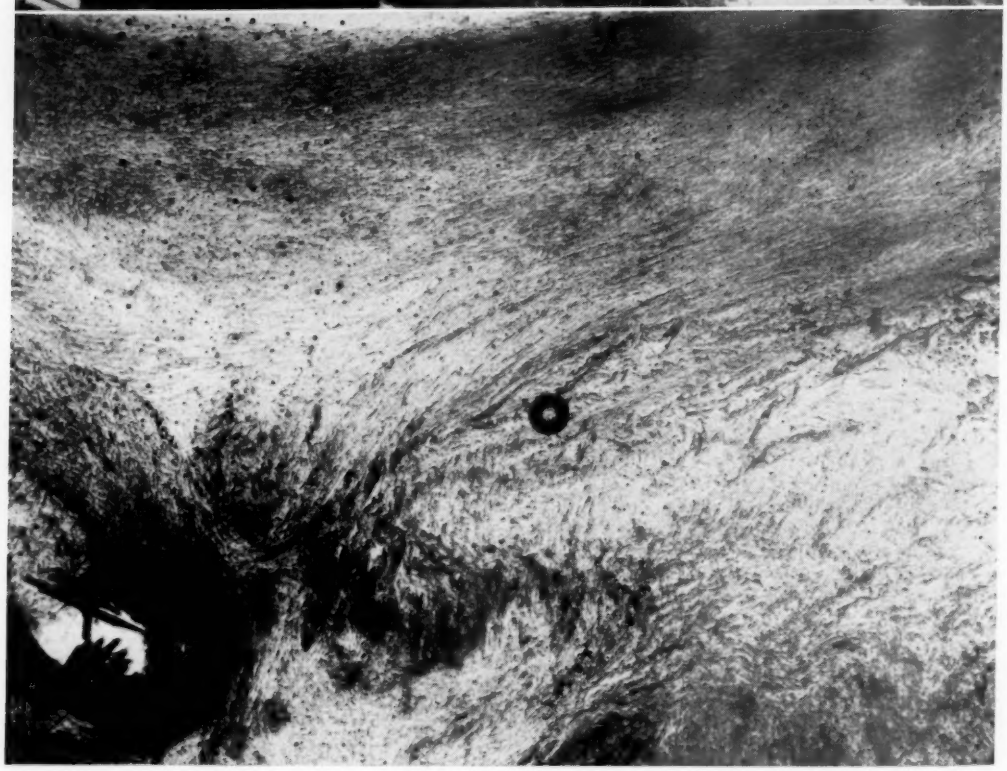

Fig. 5.

Fig. 4.—Low-power photomicrograph of canine aorta 6 months after intimal resection and 5½ months of hypercholesterolemic diet. There are well-localized areas of sudanophilia in the newly formed collagen layer (*top*). (Sudan black stain of frozen section. ×20; ⅕ off reduction.)

Fig. 5.—High-power photomicrograph of canine aorta 6 months after intimal resection and 5 months of hypercholesterolemic diet. There is diffuse sudanophilia in newly formed collagen layer (*top*) and a localized increase of stain around silk suture (*bottom left*). (Sudan black stain of frozen section. ×430; ⅕ off reduction.)

TABLE I. SUMMARY OF DATA ON ATHEROMA FORMATION AND HYPERCHOLESTEROLEMIA

DOG NUMBER	MEAN CHOLESTEROL LEVEL (MG. %)	TIME BETWEEN OPERATION AND START OF DIET	LENGTH OF TIME ON DIET	DEGREE OF ATHEROMA (1+ TO 4+)
18	184	1 day	5 months	2+
30	135	4 days	5 months	4
15	225	2 days	5 months	3
111	300	60 days	5 months	3
92	300	120 days	5 months	3
13	400	2 days	5 months	4
7	380	1 day	5 months	1
129	395	22 days	5 months	1
116	310	42 days	5½ months	4
9	350	8 days	5½ months	4

It was felt that the presence of a fresh thrombus and granulating tissue would enhance the degree of atherogenesis, but from these data (Table I), the animals placed on the diet on the forty-second, sixtieth, and one-hundred-twentieth days after operation all showed marked changes. This could imply that active lipid deposition will take place for an extended time after the initial arterial injury and beginning of the healing process.

DISCUSSION

After a perusal of the literature on atherosclerosis, it is really no surprise that the area of regenerating arterial wall is particularly prone to lipid deposition. There are a host of well-documented papers demonstrating and implying that local factors play an important part in the development of human and experimental atherosclerosis. The great mass of studies on dietary factors and lipid metabolism that have appeared since the Russian pathologist, Anitschkow, first demonstrated experimental atherosclerosis in rabbits have led many investigators away from the consideration of the organ in question. G. Lyman Duff[1] once made the comment, "The casual reader of recent literature might wonder whether some authors conceive of an atherosclerosis so independent of the substrate of the vessel wall, that it may occur in the absence of the blood vessels themselves."

In clinical practice, the natural question which arises as a result of these observations is, "How significant is lipid deposition in patients who have had thromboendarterectomy for their occlusive atherosclerosis?" Thromboendarterectomy is done in patients whose humoral factors remain unchanged postoperatively and, indeed, there is an added predisposing local arterial factor as a result of the operation.

The opportunity to study arterial segments in patients subjected to thromboendarterectomy many years previously is obviously needed. These observations should not be considered as a deterrent to the operation, since the good results of the operation far outweigh its atherogenic possibilities. Thromboendarterectomy will remain as a useful tool in atherosclerotic occlusive disease.

The observation that a mural thrombus can be a nidus for atheroma would appear to be substantiated by this study. From the pathogenetic viewpoint, the nature of the initial mural thrombus deserves further study.

SUMMARY

A series of animals subjected to experimental aortic intimal resection were rendered hypercholesterolemic during the period of aortic wall regeneration.

After 5 to 6 months of observation, examination of the major arteries revealed lipid deposition and gross atheroma only in the area of regenerated aortic wall. There was no correlation between serum cholesterol levels, time between operation and start of diet, and degree of atheroma.

Mural thrombosis probably is a precursor of atheroma formation in some instances.

Further observations of human arteries which have been subjected to endarterectomy are necessary to correlate these observations.

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UNFAVORABLE RESULTS WITH IVALON ARTERIAL GRAFTS IN DOGS

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PREVIOUS studies from our laboratory indicate that Ivalon* arterial grafts had a prohibitive occlusion rate in small arteries (internal diameter of 4 to 8 cm.), but functioned satisfactorily in larger arteries (8 to 12 mm.) during a 3-month follow-up study.[18] This report updates the observations from 6 to 24 months.

Recently, numerous papers concerning the use of Ivalon arterial grafts in man and in experimental animals have been published. Some of these reports show encouraging results[2, 3, 6, 9, 11, 13, 19, 21, 24, 25] while others reveal poor results.[1, 4, 5, 10, 12, 14-17, 20, 22, 23]

Details of construction and implantation of these 23 arterial grafts have been described in a previous publication.[18] The density and wall thickness of the Ivalon grafts were carefully controlled to give maximum strength and to provide air spaces for the ingrowth of fibrous tissue. The fates of 12 Ivalon grafts in the abdominal aorta of dogs with an internal diameter between 4 and 8 mm. and 11 Ivalon grafts in the thoracic aorta of dogs with an internal diameter between 8 and 12 mm. have been observed for periods of time ranging from 6 to 24 months postoperatively.

RESULTS

Twelve of the 23 Ivalon grafts functioned satisfactorily during the follow-up period, although one-half of the functioning grafts revealed ulceration and calcification in the pseudointima. The 11 graft failures were due to 4 occlusions and 7 aneurysms, three of which perforated. The failures were evenly distributed over the follow-up period from 6 to 24 months.

DISCUSSION

These 7 aneurysms occurred in the 11 grafts with an internal diameter of more than 8 mm. and the 4 occlusions occurred in the 12 grafts with internal diameter of less than 8 mm. This pattern of aneurysm formation in the large arteries and occlusion of the small arteries might be anticipated by the application of LaPlace's law (tension = radius × pressure). Failure of more than one-half of the Ivalon arterial grafts in these experiments strongly suggests that Ivalon is an unsuitable material for arterial grafts in dogs. Fortunately, reported successes with nylon[8] and Dacron[7] arterial grafts make further clinical use of Ivalon unnecessary.

Received for publication Oct. 29, 1958.

*Clay-Adams Company, New York, N. Y.

SUMMARY

1. Twenty-three Ivalon arterial grafts in dogs have been observed over a period of 6 to 24 months.

2. Failures resulted from either aneurysm formation or occlusion in 48 per cent of these grafts.

3. Ivalon is an unsatisfactory material for arterial grafts in the dog and probably for arterial replacement in human beings.

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FORMATION OF SUBCUTANEOUS TUNNEL IN FEMORAL ARTERIAL BYPASS OPERATIONS

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THE operative treatment for segmental occlusion of the iliac and femoral arteries has been employed frequently since arterial homografts and prostheses have been available. The bypass operation as initially described by Kunlin[4] and modified by Cockett[4] has been adopted by Linton,[4] De Bakey,[1] and others.[2, 3] It has become a well-established procedure. To obtain a functioning bypass graft, thrombosis must be eliminated. Torsion and/or compression of the bypass graft or prosthesis may result in thrombosis. These two factors may be eliminated by the formation of an adequate subcutaneous tunnel.

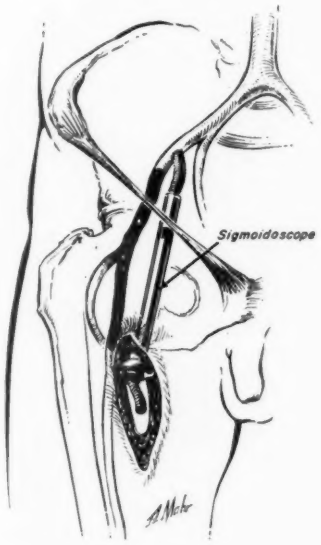

Fig. 1.

We have found that the use of a sterile 25 cm. sigmoidoscope facilitates the formation of a subcutaneous tunnel for the bypass graft. The sigmoidoscope with its obturator in place is passed through the desired subcutaneous tunnel. The graft or prosthesis which has been anastomosed at one end is then passed through the sigmoidoscope (Fig. 1). After the graft is aligned, the sigmoidoscope is removed. This allows the properly aligned graft to lie in a subcutaneous tunnel which has been dilated by the 2 cm. diameter sigmoidoscope to prevent compression of the graft or prosthesis.

Received for publication Sept. 10, 1958.

A simple effective method of forming a subcutaneous tunnel for the placement of an arterial bypass graft or prosthesis has been described. This consists of utilizing a 25 cm. sigmoidoscope as a channel through which the graft is threaded.

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ARTERITIS FOLLOWING CORRECTION OF COARCTATION OF THE AORTA

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THERE have been previous reports of arterial inflammation, necrosis, and thrombosis of smaller distal vessels following the correction of coarctation of the aorta. This has been limited to vessels below the coarctation and has developed in the immediate postoperative period. This condition has been said to be an infrequent complication, only 5 cases having been reported. We would like to report two additional cases, one of which would seem to have special interest because of its occurrence three months following the corrective procedure, after the patient had gone home and returned to normal activity. Although involvement of many vessels has been demonstrated by the pathologist, clinically the picture has been that of mesenteric thrombosis. In addition to this, in one of our cases evidence of ischemia of the spinal cord was present.

CASE REPORTS

Case 1.—R. D. M., a 5-year-old white boy, was known to have had congenital heart disease since the first days of life when he had episodes of pallor and was noted to cry and gasp after feedings. He was first admitted to John Sealy Hospital in December, 1951, on the service of Dr. Reagan Gibbs, and a diagnosis of a patent ductus with probable coarctation of the aorta was made. In addition, he had a congenital mitral stenosis and paroxysmal atrial fibrillation with periods of decompensation. The femoral pulses were scarcely palpable and the blood pressure in the arm was recorded as 120/60. An exploratory operation was initially carried out on Dec. 28, 1952, by Dr. A. W. Harrison, at which time a very definite coarctation of the aorta was found at a distance of approximately 1 cm. from the left subclavian artery, and a patent ductus was noted attached to the aortic arch just above the coarcted area. The patent ductus was doubly ligated and the repair of the coarctation was delayed until a later date. In August, 1954, the patient was readmitted for surgical repair of the coarctation of the aorta. However, shortly following the incision into the chest, the patient began to have a clonic type of generalized convulsions and the operation was discontinued. The patient was again admitted to John Sealy Hospital in April, 1955, for an upper respiratory infection, which subsequently precipitated an auricular flutter with a 1:4 block and the patient was digitalized. The patient was again admitted to the hospital on May 25, 1955, and prepared for repair of the coarctation of the aorta. On June 6 the coarcted area was identified just distal to the left subclavian artery and noted to measure approximately 5 mm. in length. The coarcted segment was mobilized, resected, and an end-to-end anastomosis was carried out. Following this procedure the patient had good pulses in the lower extremities. The blood pressure in the upper extremities was 110/80. About one week after operation it was 190/118.

Received for publication Sept. 26, 1958.

The patient had an uneventful postoperative course until the third day, when abdominal distention was present and traces of blood appeared in the stool. The blood was attributed at the time to trauma from a rectal tube. On the ninth postoperative day the patient began to complain of generalized abdominal pain and showed increasing abdominal distention. He began a febrile course and vomited dark-brown fluid. A diagnosis of mesenteric thrombosis was made and an emergency exploratory laparotomy was performed by Dr. R. M. Moore. The operative findings were described as follows: "The upper few feet of jejunum appeared normal; then, descending the jejunum, one found at 2 to 6 inch intervals bands of darkish discoloration extending on to the mesenteric border of the bowel. The central ileum was most involved, there being segments of advanced gangrene in this region with thin, nearly transparent, greenish intestinal wall. The terminal few inches of ileum was normal." The involved intestine was resected, measuring 107 cm. in total length, and an end-to-end anastomosis was carried out. The pathological examination of the vascular tree in the mesentery was described as follows: "Sections of the mesentery removed from the small bowel showed both the veins and the arteries to be thrombosed. There is a marked inflammatory infiltrate present in both vessels, that is more marked in the arteries." The patient recovered after a stormy postoperative course and is alive at this time with no further abdominal symptoms; however, he remains a cardiac problem.

CASE 2.—F. C., a 35-year-old white man, was admitted to John Sealy Hospital, on July 12, 1958. He had been a known hypertensive for many years and when his systolic blood pressure finally reached above 300 mm. Hg, a coarctation of the aorta was discovered. This was surgically corrected by a prosthetic bypass made under the supervision of Dr. Denton Cooley at another hospital about three months before. The patient had a normal convalescence and was discharged one week postoperatively. He then returned home where he continued to convalesce uneventfully for another month. After that time he returned to his usual occupation with the city maintenance department. Sixteen days prior to his hospitalization here, he experienced a sharp pain in the mid-abdomen to the right of the umbilicus. This pain was constant; however, it disappeared some 30 to 45 minutes after its onset and he developed no more symptoms. Three days later he awoke suddenly one morning with nausea, vomiting, and diarrhea, and mid-abdominal pain again. Although he improved, the symptoms again returned the following day while the patient was at work, only to subside again that evening. The patient was symptom-free until 10 days prior to his admission here, when he again developed nausea and vomiting with abdominal pain and was hospitalized by his local physician in another city. He was treated with intravenous fluids and gastric section and improved during the six days of hospitalization and was put on a soft diet. An x-ray workup was carried out, including an upper gastrointestinal series and a barium enema, all of which were completely negative. The patient was subsequently discharged. However, he again developed symptoms the following day and was referred to John Sealy Hospital for further evaluation.

When seen in the emergency room the patient was in mild distress with some abdominal pain and stated that he had noted increasing abdominal distention for the past two to three days. He had been tolerating a liquid diet prior to his admission and had had daily bowel movements. Physical examination showed a blood pressure in the right arm of 190/110 and in the left arm of 150/110. There was no evidence of hypertensive retinopathy. Examination of the chest was essentially negative except that there was a Grade 3 systolic murmur heard best in the third left intercostal space at the midclavicular line. The abdomen was moderately distended and no masses were palpable; bowel sounds were very hypoactive; there was moderate periumbilical tenderness to deep palpation. Pulses were present throughout both lower extremities; however, they were markedly diminished from the normal. Blood pressures in the lower extremities were recorded as 100-110/70. A dermatitis medicamentosa which generally covered the body was attributed to penicillin sensitivity. X-rays of the abdomen were essentially

negative except for showing one small segment of intestinal gas in the mid-abdomen. Complete blood count revealed a moderate leukocytosis with left shift. The admission diagnosis was necrotizing mesenteric arteritis secondary to the coarctation repair.

The patient improved some following admission and took surgical liquids with no difficulty and had normal bowel movements intermittently. However, on the day following admission the patient still complained of some abdominal pain and was placed on gastric suction and intravenous fluids. His condition continued essentially unchanged until early in the morning of the second day following admission when he began to complain of an inability to void. The patient was encouraged to stand and was very unsteady on his feet and unable to walk or stand without support. Neurological examination at the time showed the deep tendon reflexes to be diminished bilaterally but equal, with no other pathological reflexes noted. During the day the patient deteriorated markedly, with an elevation of his pulse rate, and increasing leukocytosis with left shift. He developed a flaccid paralysis of the lower extremities with an ascending sensory loss, persistent

Fig. 1.—Case 2. Aortogram showing patent aorta and mesenteric vessels.

atony of the bladder, an acute diffuse abdominal tenderness with absent bowel sounds, a questionable diminishing of the quality of the pulses in the lower extremities, and a rising serum amylase. Due to the progression of neurological signs along with the progression of abdominal signs, the possibility of a thrombosis or a dissecting aneurysm starting at the site of the coarctation repair was considered, and retrograde aortography was done through the left brachial artery. This revealed a good runoff through a bypass around the coarctation with filling of the abdominal aorta and the superior and inferior mesenteric vessels on x-ray (Fig. 1). A peritoneal tap was done and revealed amber, cloudy fluid which had a white blood count of 12,000 and 720 units of amylase. The decision was made to explore the patient's abdomen on the evening of the third day

following admission, with the preoperative diagnosis of gangrenous bowel secondary to progressive necrotizing arteritis, secondary to repair of coarctation of the aorta. Exploration was subsequently done and the entire small bowel from the ligament of Treitz to the ileocecal valve showed patchy areas of gangrenous change, some with impending perforation. The right colon also showed patchy areas of gangrenous change, and the left colon and stomach and duodenum were noted to be very pale and markedly ischemic, and would not bleed when incised through the serosa. It was felt that the disease had

Fig. 2.

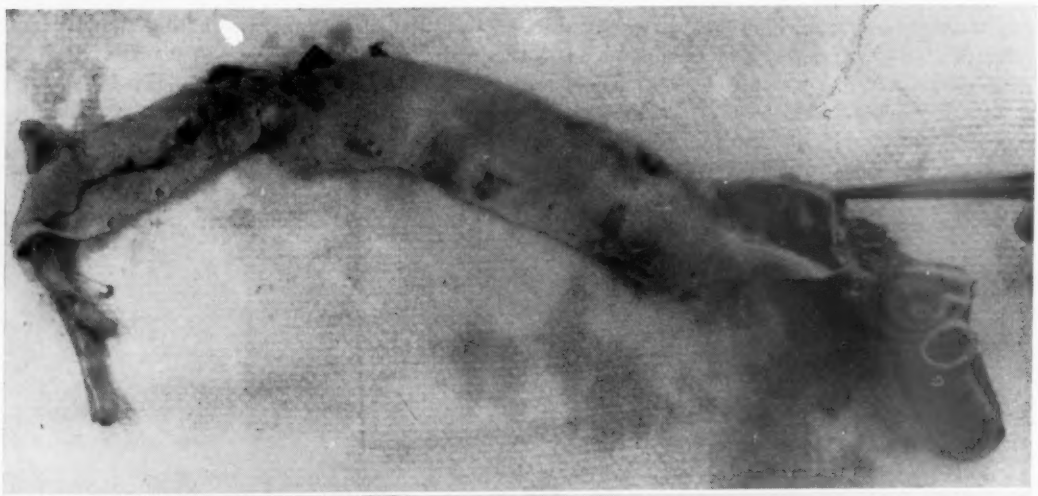


Fig. 3.

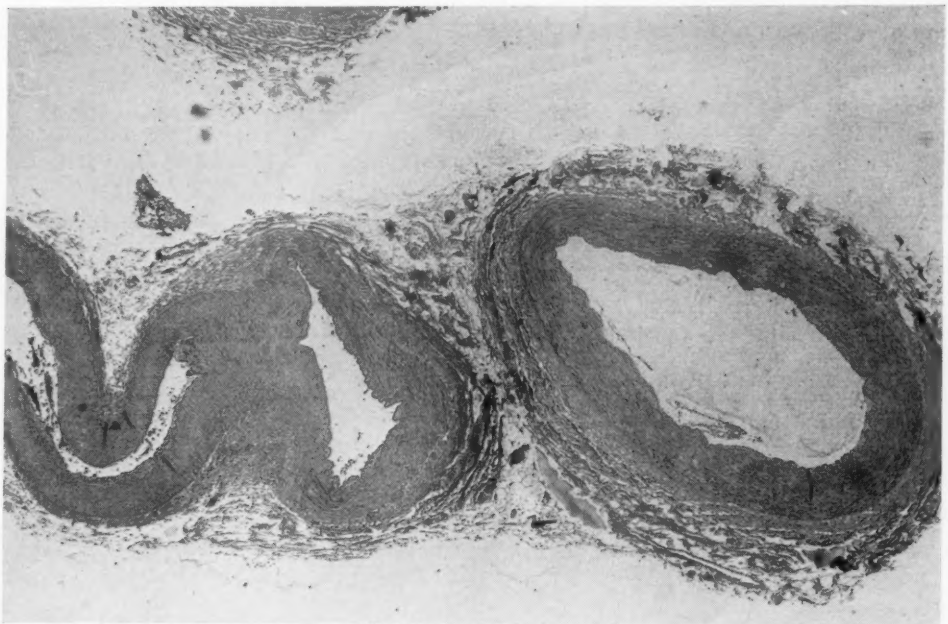
Fig 2.—Case 2. Aorta. Opening of graft lumen distal to coarctation is seen beneath tip of pointer.

Fig. 3.—Case 2. Aorta. Corrugated exterior of graft is visible.

progressed too far to be amenable to any surgical therapy, and a biopsy of the jejunal mesentery was taken, and the patient's abdomen closed. A progressive downhill course ensued postoperatively, and the patient expired on the fifth day following admission.

Examination of the biopsied mesentery by our surgical pathologist revealed a necrotizing arteritis consistent with that found following repair of coarctation of the aorta.

Fig. 4.



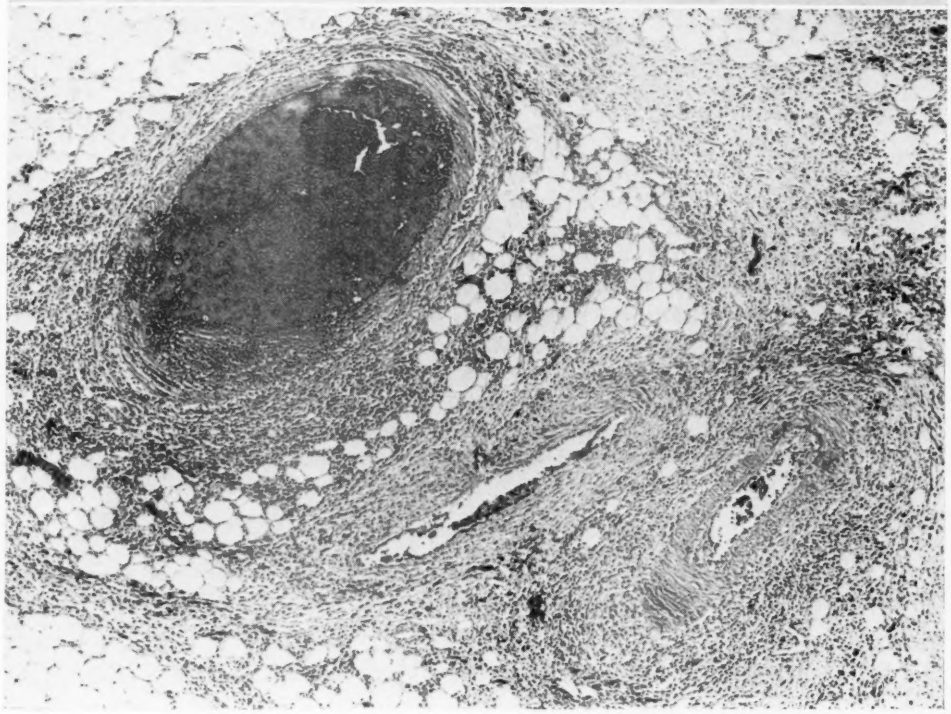


Fig. 5.

Fig. 4.—Case 2. Photomicrograph of large mesenteric arteries. Note absence of occlusion or inflammation in vessel wall. (Hematoxylin and eosin stain; ×18.)

Fig. 5.—Case 2. Photomicrograph of mesenteric endarteritis near bowel. Note inflammation and necrosis of arterial wall with thrombosis. (Hematoxylin and eosin stain; ×42.)

TABLE I. MESENTERIC ARTERITIS FOLLOWING

CASES		AGE (YR.)	SEX	RACE	BLOOD PRESSURE			
					ARMS		LEGS	
					PREOP.	POSTOP.	PREOP.	POSTOP.
Benson and Sealy[2]	1.	22	Male	Negro	190-215 / 60-0	220-160 / 80	104-120 / 80-0	Strong pulses
	2.	4	Male	White	148 / 84	118 / 80	98 / 65	225 / 180
Lober and Lillehei[3]	3.	12	Male	White	160 / 98	150 / 80	Weak pulses	Strong pulses
	4.	46	Male	White	200 / 100	—	None	—
Perez-Alvarez and Oudkerk[4]	5.	5	Male	White	150 / 70	140 / 80	None	Strong pulses
Singleton Mc Ginnis and Eason	6.	5	Male	White	120 / 60	110 190 / 80 118	Faint pulse	Good pulse
	7.	35	Male	White	280 / 130	190-150 / 110	—	100-110 / 70

The postmortem findings were as follows: The heart weighed 500 grams, most of the enlargement being due to a greatly hypertrophied left ventricle. The coronary arteries were patent but markedly sclerotic. The aorta contained the synthetic prosthesis which was patent and revealed no evidence of thrombus formation (Figs. 2 and 3). The circumference of the aorta in the mid-portion of the arch was 6.2 cm. Below the area of coarctation it was moderately hypoplastic, the circumference at the level of the renal arteries being 3.2 cm. and at the bifurcation of the iliacs 2.5 cm. The lungs were not remarkable except for moderate congestion. The most striking findings were in the abdominal cavity. There were 500 c.c. of a hemorrhagic fluid and a generalized peritonitis. All of the small bowel from the mid-portion of the duodenum and one-third of the ascending colon was distended and gangrenous. The stomach and first half of the duodenum were not involved in the gangrenous process and the other abdominal organs appeared to be grossly normal. The mesenteric artery and its larger branches were checked and found to be patent, with no evidence of thrombosis. There were no areas of infarction in the mesentery, but the cut surfaces near the intestinal wall revealed thrombosis of the small vessels. The spinal cord revealed signs of myelomalacia from the level of T_{10} down to the conus. The anterior spinal artery was patent but many of the epidural veins were thrombosed.

Microscopically there was a necrotizing arteritis of most of the small arteries of the mesentery and small intestine (Fig. 5). This was characterized by marked fibrinoid necrosis of the tunica media, with thrombus formation and a marked perivascular inflammatory reaction with round and segmented cells. There was marked necrosis of the

REPAIR OF COARCTATION OF AORTA

ASSOCIATED VASCULAR ABNORMALITIES	OPERATION FOR COARCTATION	ONSET OF ARTERITIS	ABDOMINAL EXPLORATION	RESULT
Bicuspid insufficient aortic valve	Resection below arch with end-to-end anastomosis	3rd postop. day; abdominal pain	10th postop. day; infarction of small bowel and first part of colon	Died during operation
Patent ductus	Ligation of patent ductus; resection with end-to-end anastomosis	3rd postop. day; abdominal pain	16th postop. day; resection of 24 inches of necrotic bowel	Recovered
Bicuspid aortic valve	Resection with end-to-end anastomosis	4th postop. day; abdominal pain	Ruptured splenic artery aneurysm; resection of 300 cm. of necrotic small bowel	Died on 23rd postop. day; multiple small aneurysms at necropsy
Enlarged left ventricle; apical sytolic murmur	Resection with end-to-end anastomosis	8th postop. day; vomiting and fever	10th postop, day; resection of 38 cm. of small bowel	Recovered
None	Resection with end-to-end anastomosis distal to subclavian artery	8th postop. day; abdominal distress	11th postop. day; mesenteric adenitis; 20th postop. day; resection of gangrenous bowel	Died 21st postop. day; bowel leakage
Patent ductus; mitral stenosis	Resection with end-to-end anastomosis distal to subclavian artery	3rd postop. day; distention	9th postop. day; resection of 107 cm. of small bowel	Recovered
Enlarged left ventricle	Bypass graft	Pain in abdomen 3 months after operation	19 days after onset of symptoms; gangrene and ischemia of entire gastrointestinal tract; no resection done	Died 21 days after onset of symptoms

small intestine. Sections of the mesenteric artery and some of its larger branches revealed a few small areas of fibrinoid necrosis in the tunica media with no inflammatory reaction and no intimal involvement (Fig. 4). There was involvement of isolated small arteries in the kidneys, adrenals, and pancreas with medial fibrinoid necrosis and marked inflammatory reactions. The arteries of the esophagus, stomach, and spleen were essentially normal. Sections of the spinal cord revealed recent ischemic necrosis of almost the entire cross section of the cord between T_{10} and L_1. The changes were most marked in the distribution of the anterior spinal artery although sections of the artery reveal no thrombosis or inflammatory reaction.

DISCUSSION

Following the demonstration that coarctation of the aorta could be successfully treated surgically by Crafoord and Gross, many surgeons have reported their experiences in attempting to correct this condition. The complications following resection of coarctation of the aorta were usually due to technical operative difficulties such as dehiscence of the aortic suture line, or to preexisting cardiovascular disease such as cerebral hemorrhage and cardiac failure often associated with other congenital anomalies. Perez-Alvarez and Oudkerk[4] have reported a mortality rate of 5 per cent, with two fatalities out of 40 patients operated on. One of the deaths was due to dehiscence of the aortic suture

line which was infected, and the other due to acute necrotizing arteritis of the abdominal organs developing late in the postoperative period. Sealy[5] in 1953 reported the correction of coarctation in 22 cases. In the first 19 cases there were no deaths. The twentieth patient died of a rupture of the aortic suture line. The only postoperative complication that occurred in the surviving patients was a subarachnoid hemorrhage on the fourth postoperative day. The twenty-first patient, a man 26 years of age, on the tenth postoperative day developed abdominal symptoms and died while being explored for mesenteric thrombosis. While the jejunum and first part of the ileum were found to be edematous and markedly cyanotic, it was noted that the mesenteric artery and its subdivisions pulsated and the mesentery veins were patent. Autopsy revealed inflammation of the small arteries and arterioles confined to the body area supplied by the aorta below the coarctation. There were numerous infarcts in the liver, spleen, and intestine. There were no emboli to the mesenteric artery or thrombi in the mesenteric veins. The suture line in the aorta was healed and thrombi were not present either in this location or in the scarred valve. Lober and Lillehei[3] have reported two cases of necrotizing panarteritis following repair of coarctation of the aorta. One case recovered after small bowel resection; the other died following small bowel resection. In addition, this case had a ruptured aneurysm of the splenic artery necessitating splenectomy. Benson and Sealy[2] reported in 1956 an additional patient who survived after a small bowel resection. Although arteritis has been considered as an unusual and infrequent complication, certainly in the experience of some surgeons this has been one of the major problems to be faced in the correction of coarctation.

The pathogenesis of arterial necrosis following aortic resection for coarctation has been well discussed by Benson and Sealy.[2] They have found that the lesions were limited to arteries leaving the aorta below the level of the coarctation. These were considered to be primarily the results of changes in circulatory dynamics following operation. The abdominal vessels were subjected to an elevated systolic pressure and consequently a larger, sharply increased pulse pressure. This probably resulted in greater constant distention of the arteries upon which was superimposed frequent, rapid, further distention by the markedly changed pulse pressure. Lober and Lillehei[3] have felt that the necrotizing panarteritis seen in these cases is indistinguishable from periarteritis nodosa. Besides the effects of hypertension, hypersensitivity, increased salt in the diet, allergic reaction, steroids, and other congenital anomalies have also been considered as factors in the etiology of this condition.

Adams and Van Geertruyden[1] have reviewed neurological complications of aortic surgery, including 11 cases following operations for coarctation of the aorta. No mention of arteritis of the vessels supplying the spinal cord was noted and we have found no other cases reported in the literature.

In looking over the cases of arteritis (Table I) following repair of coarctation, it will be noted that while many vessels below the point of coarctation have shown histological evidence of involvement, the terminal portions of the vessels have been the area of actual occlusion, and with the exception of our one case have symptomatically involved only the superior mesenteric system.

It will be seen that again with the exception of our last case, the onset of symptoms occurred from the third to the eighth postoperative day although abdominal exploration did not take place until the second to the nineteenth day following the onset of such symptoms. One receives the impression that earlier laparotomy might have been desirable in these patients, though one patient who underwent exploratory operation two days after onset of symptoms showed only mesenteric lymphadenitis followed by gangrenous bowel discovered at a second laparotomy nine days later. There were four deaths out of the seven cases.

It may also be noted that there were no secondary attacks of arteritis that could be detected clinically in the reported cases.

SUMMARY

Two cases of arteritis following correction of coarctation of the aorta are reported together with a review of five other cases taken from the literature. One case is of special interest in that the symptoms of arteritis appeared after the immediate postoperative period and involved the spinal cord as well as the gastrointestinal tract.

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LINEAR POLYETHYLENE, A NEW SUTURE MATERIAL FOR ARTERIAL ANASTOMOSIS

An Experimental Study

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LINEAR polyethylene is a new synthetic material whose properties have suggested its employment as a suture material. This report, therefore, concerns a comparison study of 5-0 linear polyethylene and 5-0 braided arterial silk with respect to the former's applicability for use principally in small artery anastomoses.

TENSILE STRENGTH

Tensile strength studies were performed using an inclined plane Scott tensiometer. The 5-0 polyethylene arterial suture, as received from the manufacturers, was divided into 10 cm. segments from each of 16 sutures. The tensile strength of eight of these segments was determined and measured from a high of 1,060 Gm. to a low of 760, the average being 935 Gm. The remaining 8 segments were placed in thioglycolate culture tubes which contained a mixed bacterial flora that had been obtained from a recent surgical wound infection. The suture segments were permitted to remain in this media for 4 days, at which time their tensile strength was measured. As a means of comparison, 5-0 braided silk was investigated under similar conditions. The results of these experiments are tabulated in Table I.

Table I. Tensile Strength Loss of 5-0 Linear Polyethylene and Silk Following Immersion in Contaminated Culture Media for 4 Days

Suture Material	Average Tensile Strength	Average Tensile Strength Following 4 Days' Immersion in Contaminated Culture
Linear polyethylene 5-0	935 Gm.	930 Gm.
Silk 5-0 (braided)	700 Gm.	620 Gm.

It is to be noted that linear polyethylene incurred a tensile strength loss of only 5 Gm. compared to 80 Gm. by silk.

In addition, 20 segments of 5-0 linear polyethylene were steam autoclaved from one to four times by conventional surgical sterilizing methods. In only 4 instances was the tensile strength loss below the average of 935 Gm., and this

We wish to acknowledge the cooperation of the American Cyanamid Company, Danbury, Conn., Harold D. Evans, Jr., Medical Director, who supplied the linear polyethylene suture material for use in this study.

Received for publication Oct. 16, 1958.

occurred when the 4 sutures were sterilized three times. Oddly enough the 5 sutures sterilized four times did not demonstrate a decrease in tensile strength. When braided arterial silk was investigated under similar conditions a decrease in tensile strength was noted and averaged 40 Gm. following the fourth time it was subjected to steam sterilization.

Next, segments of 5-0 linear polyethylene and 5-0 braided arterial silk sutures were embedded in the strap muscles of mongrel dogs. Beginning at intervals of 2, 5, 10, 15, 20, 25, and 30 days, the sutures were removed and tensile strength measurements made. A total of 14 experiments was performed for each suture. In each case, both linear polyethylene and silk showed a decrease in their tensile strength characteristics. The tensile strength changes incurred by the former were somewhat erratic; however, in no instance was it less than that of silk (Fig. 1).

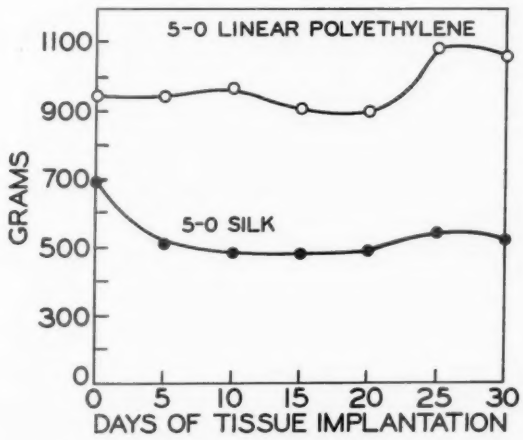


Fig. 1.—The effect of tissue implantation on the tensile strength of 5-0 braided arterial silk and 5-0 linear polyethylene. The erratic tensile strength measurement of the latter material is unexplained.

Last, the tensiometer was used to measure the change in tensile strength as well as the knot "slippage" of both silk and linear polyethylene when conventional surgical knots were introduced into their structure. The results are shown graphically in Fig. 2. It is to be noted that linear polyethylene segments joined by square knots or surgeon's knots invariably slipped at measurements between 200 and 600 Gm. When a double square knot or a surgeon's knot with an extra loop was used, these knots remained secure; however, the tensile strength of the material was markedly decreased from the average normal of 935 Gm. Still linear polyethylene was superior in that its tensile strength with the presence of a knot was greater than that of silk.

VASCULAR EXPERIMENTS

Thirty adult mongrel dogs were anesthetized with intravenous Nembutal and, employing sterile technique, the carotid and/or femoral arteries were isolated and divided. Artery continuity was re-established by anastomosing the cut ends according to the Carrel suture technique, using 5-0 linear polyethylene and braided 5-0 arterial silk. A total of 30 anastomoses was employed

for each suture material. Beginning on the second postoperative day and up to 30 days, the animals were sacrificed at which time the anastomosed artery segments were excised and the patency of the lumens was determined. In addition, alternate artery segments were distended with saline to determine the pressure required to rupture the anastomoses. The artery segments were then bivalved in their longitudinal axis, placed in 10 per cent formalin, and later stained with hematoxylin and eosin for microscopic examination.

The results of the animal experiments are as follows: Gross examination of the anastomotic sites following their completion, as well as after sacrifice of the animal, suggested that little or no evidence of stenosis occurred at the site of the anastomosis with either silk or linear polyethylene. Furthermore, 16 of the 60 anastomoses were occluded or partially occluded: 9 with silk and 7 with linear polyethylene.

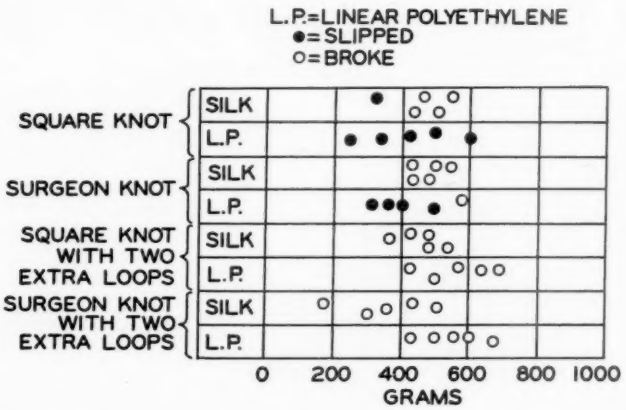


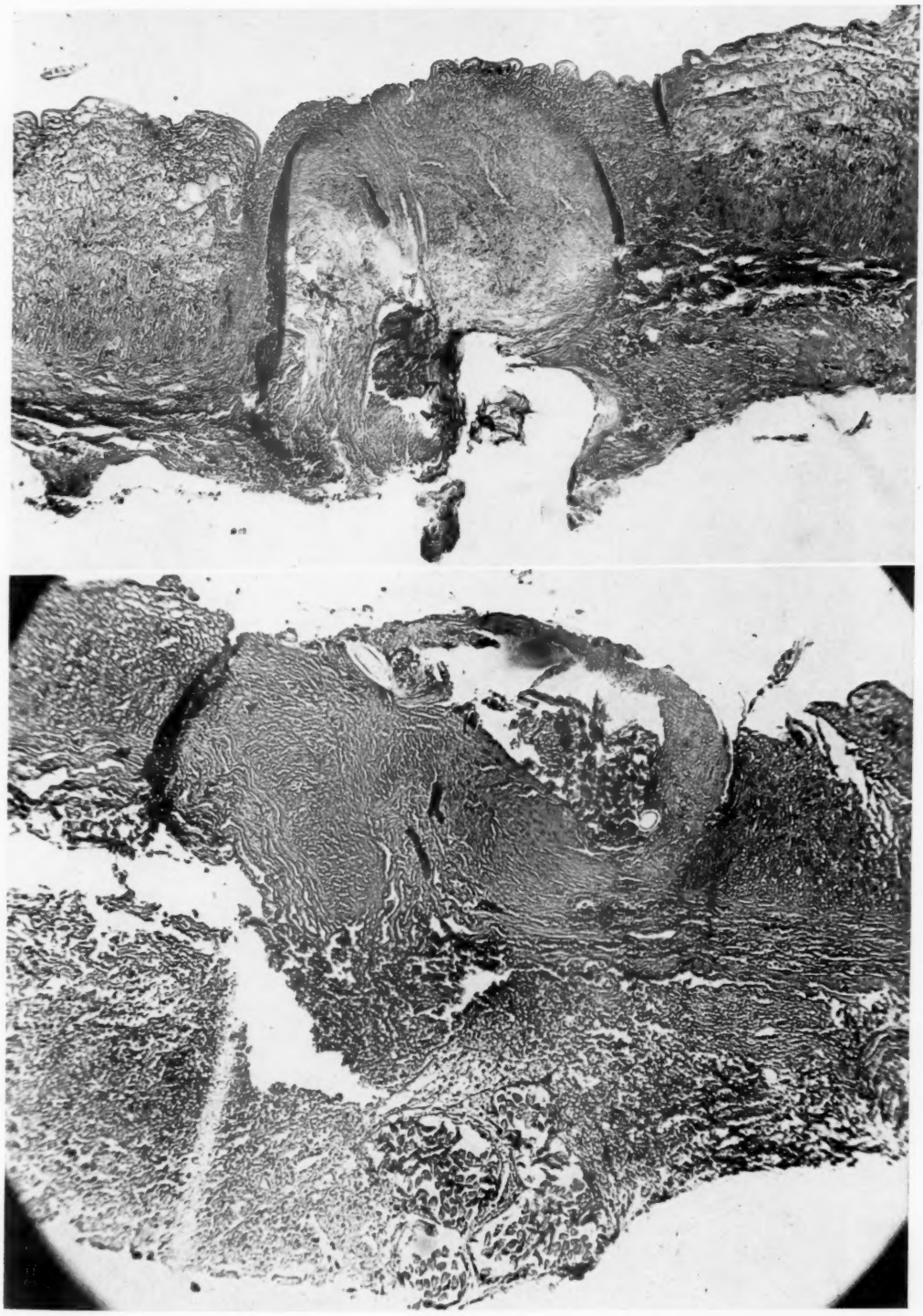
Fig. 2.—Tensile strength and knot security of 5-0 braided arterial silk and 5-0 linear polyethylene where four different knots were employed to secure the suture. All tests were made with the Scott inclined plane tensiometer. Circles represent breaking point of suture. Dots indicate knot slipped or became untied. Measurements are in grams.

The pressure studies demonstrated the remarkable ability of sutured arteries to withstand intraluminal pressure much in excess of normal evidence of rupture. In each instance, and beginning with the second day, the linear polyethylene as well as the silk-fashioned artery anastomoses withstood pressure up to 250 mm. Hg without rupturing. However, air leaks developed at the sit of the anastomoses fashioned with linear polyethylene at pressures of 140 to 190 mm. Hg, a finding that seldom occurred with those constructed with silk. This phenomenon appeared directly related to the increased tissue response initiated by silk about the line of anastomoses.

MICROSCOPIC STUDY

The essential comparative histologic findings were as follows: From the second to tenth days, the inflammatory response as measured by the polymorphonuclear cells and the degree of edema was most marked in the artery wall of the silk-fashioned anastomoses (Figs. 3, *A* and *B*). From the tenth to twentieth days, the acute inflammatory cell response gradually receded and was replaced by fibroblasts, mononuclear cells, and giant cells, and again

A.



B.

Fig. 3.—Microscopic section of the anastomotic site showing tissue response at 48 hours: (*A*) linear polyethylene and (*B*) silk. Note the increased edema and periadventitial collection of polymorphonuclear cells about the silk-fashioned anastomoses. (×50, hematoxylin and eosin.)

A.

B.

Fig. 4.—Photomicrograph showing tissue response of an artery anastomosis of 30 days' duration: (*A*) linear polyethylene and (*B*) silk. Note minimal degree of fibroplasia incurred by linear polyethylene in comparison with silk. (×50, ⅛ off reduction; hematoxylin and eosin.)

this was most marked in arteries where silk was employed. From the twentieth to thirtieth days, fibroplasia was increased while the cellular reaction was decreased but, again, this response to linear polyethylene was relatively benign when compared with silk (Fig. 4, *A* and *B*).

SURGICAL MANAGEABILITY

Linear polyethylene is a transparent, smooth, somewhat rigid suture material in comparison to silk and, as such, one becomes quite impressed by its ease of manageability. This was principally noted by its glide effect when passing through the artery wall, giving one the sense of little or no resistance being offered to its presence. Furthermore, the bothersome catching on residual adventitia was a less frequent occurrence when linear polyethylene was employed.

In addition, linear polyethylene did not absorb tissue juices and blood and, subsequently, did not become adherent to adjacent skin towels, a feature that was quite common when silk was used.

However, linear polyethylene had certain disadvantages which were principally concerned with the problem of knot "slippage" when surgical knots were introduced into its structure. In each instance, careful attention had to be exercised in properly "laying down" each loop of the knot otherwise the knot had a tendency to spring apart. This problem was circumvented by using double loops following a conventional square knot or a surgeon's knot.

Inasmuch as linear polyethylene is transparent, difficulty was encountered in removing a suture that had inadvertently become crossed with another. This problem has been corrected by the introduction of pigment material into the suture proper.

Following establishment of blood flow, the anastomoses created with linear polyethylene resulted in bleeding at the suture line much in excess of those constructed with silk. However, gentle pressure on the suture line with surgical sponges corrected this problem quite easily.

DISCUSSION

Linear polyethylene suture material fulfills many of the requirements desired of an arterial suture and particularly when it is employed in small artery surgery. The advantages of this suture over conventional silk are manifested principally by its decreased tissue response and, in some respects, by its ease of handling.

To many observers[1, 2] the tissue response elicited by a suture material as determined by edema, cellular infiltrations, and fibroplasia is the cardinal factor in selecting a suture for general surgical use. Suffice it to say, when a suture material is used for anastomosing small arteries, the tissue response gains further importance, for, with the advent of edema and cellular infiltrations in the region of the anastomoses, disturbance to the normal flow pattern is introduced which, in itself, favors intravascular thrombosis. In addition, the cumulative local effect resulting from this tissue reaction may act as a nidus for the formation of a thrombus.

The problem of tensile strength in a suture material needs little emphasis, and to discuss it further would only be a repetition of a well-known fact. Linear polyethylene was superior to silk in this regard; however, the introduction of surgical knots into its structure resulted in significant and somewhat disturbing loss of tensile strength. In addition, the necessity of employing double square knots and extra loops when linear polyethylene was used requires emphasis as a square or surgeon's knot invariably slipped at measurements well below the breaking point.

At present, sufficient time has not elapsed to determine if this product is noncarcinogenic. However, from a perusal of the literature we have been unable to find a case of malignancy that has occurred from using products related to linear polyethylene, namely, cellophane and polyethylene.

It is quite apparent that of the available suture material being employed today there is no ideal suture. As such, compromises of one or more requirements demanded of a suture have to be made in selecting one for the condition at hand. In the field of vascular surgery this problem takes on greater importance, and even more so when small arteries whose diameters are less than 5 mm. are to be surgically approached. If our knowledge of wound healing is to be applied correctly, it seems reasonable that a suture material like linear polyethylene, with its ease of handling which, in itself, suggests less trauma to the artery, and whose presence in tissue introduces but a minimal tissue response, is to be preferred to silk and other materials whose characteristics with respect to these factors are not as refined.

SUMMARY

A laboratory investigation of linear polyethylene arterial suture has been presented. It is concluded that 5-0 linear polyethylene is a satisfactory arterial suture when employed for small artery anastomoses.

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EVALUATION OF BLOOD LOSSES DURING SURGICAL OPERATIONS

Comparison of the Gravimetric Method With the Blood Volume Determination

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THE importance of the loss of blood in the course of a surgical operation and the consequences arising from failure to replace it[1, 5, 6, 8, 11, 15, 17, 19, 20, 21, 22, 24, 25, 27] have been well established. The individual judgment of the surgeon is in itself inadequate to evaluate properly the blood lost during an operation.[1, 20, 22] The determination of the hematocrit, hemoglobin, plasma volume, and total hemoglobin, have also proved inadequate.[6, 8, 16, 19, 24] The calorimetric method has the disadvantage of requiring a certain amount of time for its determination; therefore, it could not be used in the course of an operation.[6, 11, 17, 21, 27] The ideal method, from the standpoint of accuracy, would be the determination of the blood volume, although it also presents the drawback of being time-consuming; thus the impossibility of applying it while operating.

The gravimetric method for determination of blood losses in surgical operations constitutes a simple medium: it does not require special equipment and can be performed by the anesthetist in a progressive manner in the course of the operation. Nevertheless, this method offers several sources of error, in the sense that the loss of blood occurred in the surgical operation, as calculated by weighing the stained gauze, is in reality less than the actual amount of blood lost. This is due to several factors: evaporation (even though the weighing operation is carried out immediately); loss of blood in the site where the surgeon disposes of the gauzes, loss of blood in the surgeon's coat and gloves, operative field clothes, etc. Usually, it is the anesthetist who makes the estimate of blood lost and here again intervenes the subjective factor on which we have already commented. It is also a common practice to assign a fixed amount, as for example from 50 to 100 c.c. to the amount of blood lost. The latter is subject to criticism, since it is logical to assure that the greater the loss of blood, the greater also the unweighed losses.

The purpose of this paper is to make a comparison between the blood loss as calculated by means of the determination of the blood volume, before and after the operation, and the estimated blood loss by means of the gravimetric method. By studying their correlation, it might become possible to establish an equation by which the amount of loss in weighed gauzes may be determined, thus obtaining the actual amount of blood lost during the surgical operation.

Received for publication Sept. 23, 1958.

MATERIAL AND METHODS

Twenty-nine patients on whom ultraradical mastectomy has been performed as treatment of cancer of the breast have been studied. General anesthesia was employed. Nine of these patients were discarded because of deficient peripheric venous system, postoperative hypotension, or immediate postoperative loss of blood appreciable by suction. Ultraradical mastectomy was chosen in view of the fact that in this type of operation losses of blood occur in variable quantities (500 to 3,000 c.c.).

All the operations were performed by the same surgeon and the same anesthesia team, in order to eliminate as much as possible the subjective influence involved.

Two determinations of blood volume were carried out, the first of them a few hours prior to the operation, the other one immediately after.

The Gibson and Evans technique, with the modifications suggested by Nitshe[18] and Gregersen,[13] was used in the determination of the plasma volume. These determinations were effected in serum, using a Coleman Jr. spectrophotometer at 620 mμ. The total blood volume was determined by the hematocrit obtained from blood of the femoral artery, centrifugalized at 1,500 g. for a period of 30 minutes.

No correction for plasma included in the sedimental volume was made. In the course of the operation, the patients received a total blood transfusion as well as a solution of glucose serum at 5 per cent in quantities ranging from 500 to 1,000 c.c. It is a known fact that the administration of the latter, even at a quick pace, does not alter the blood volume.[4]

The blood loss during the operation was determined on the basis of the difference in blood volume pre- and postoperatively, plus the volume of transfused blood. In the evaluation of the volume of transfused blood, the volume of A.C.D. anticoagulant solution which each bottle of blood contains, was not taken into account, in view of the fact that it is not believed to affect the blood volume in any way.[4] In order to study the possible error of our technique, determinations of the blood volume were effected following the same technique in four patients who had not been operated on and who were in a fairly stable condition. The differences between both blood volumes (taken within an interval comparable to the one of the operated patients) were 0.87, 3.0, 1.2, and 1.5 per cent, respectively. This fact coincides with the pertinent literature.[2] The determination of blood loss by the gravimetric method[25] was effected by employing exclusively pieces of cloth (gauzes, etc.), dry, of a known weight. The gauzes were grouped in packages of a known number, in order to know the average weight of each type and later utilize it in the calculations. The stability in the weight of the gauzes was demonstrated by Bonica and Lyter,[5] who proved the possibility of error to be less than 1 per cent when weighing several hundred gauzes. The gauzes must be weighed immediately after use, because if they are weighed all at the same time at the end of the operation, an error in weight is likely to result due to evaporation[22]

(Table I). No corrections on account of the specific density of the blood were made, inasmuch as the latter fluctuates around 1.050.[22] A pan scale with a 5 Gm. sensitiveness was used. Only the loss of blood as weighed in the gauzes was taken into account, and not the blood lost in gloves, aprons, and other garments. The method of blood aspiration in the operative field was not employed. The statistical study was conducted along the lines of the established system.[9, 26, 28]

TABLE I. DIFFERENCE IN WEIGHT DUE TO VAPORIZATION

OPERATION	WEIGHT OF SPONGES IMMEDIATELY AFTER OPERATION (GM.)	WEIGHT OF SPONGES AT THE END OF OPERATION (GM.)	WEIGHT DIFFERENCE (GM.) VAPORIZATION
1. Radical mastectomy	916	714	202
2. Radical mastectomy	1,170	1,134	36
3. Radical mastectomy	944	812	132
4. Radical mastectomy	658	548	110
5. Radical mastectomy	772	500	272
6. Hysterectomy	1,214	1,194	20
7. Hysterectomy	592	500	92

RESULTS AND DISCUSSION

The ideal method for determination of the blood volume would be to make a direct determination of the cell mass and the plasma volume. We have determined the plasma volume directly by means of T-1824[7, 10, 14, 23] and the total cell volume by means of the hematocrit. This method of determining the total cell volume could be subject to criticism on the grounds that the total hematocrit of the body is not the same as the peripheral hematocrit, the former being 7.5 per cent lower.[3, 12] Owing to this, the blood volume determined by the peripheral hematocrit is higher that the blood volume found by directly determining the cell volume and the plasma volume. However, this difference is constant in the same sense, and loses significance when comparisons are made in the same subject of the blood volumes determined with a similar technique.

The results obtained in the 20 satisfactory experiments are given in Table II. A summary of the results of the statistical study is given in Table III.

With these results two dispersion diagrams were constructed. The first one correlated the operative blood loss not restored (difference between the pre- and the postoperative blood volume) with the difference between the pre- and the postoperative hematocrit. It can be seen (Fig. 1) that there is no correlation between both data, and that the hematocrit increases in some patients in spite of having significant blood losses that have not been restored.

This is to be expected, since some patients receive transfusions with blood whose hematocrit is higher than the preoperative hematocrit. This graph ratifies the well-known fact that it is impossible to determine the operative blood loss by means of the hematocrit. Fig. 2 shows the existing correlation between the operative blood loss determined by the gravimetric method and

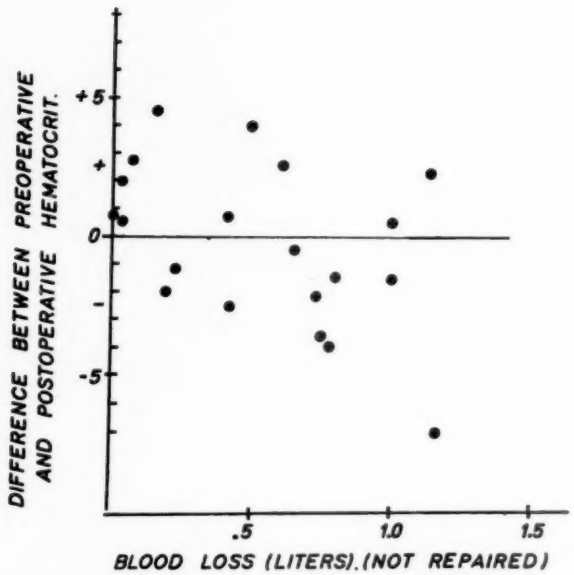

Fig. 1.—Diagram showing that there is no correlation between the difference in the preoperative and postoperative hematocrit and the blood loss during the surgical operation which is not restored.

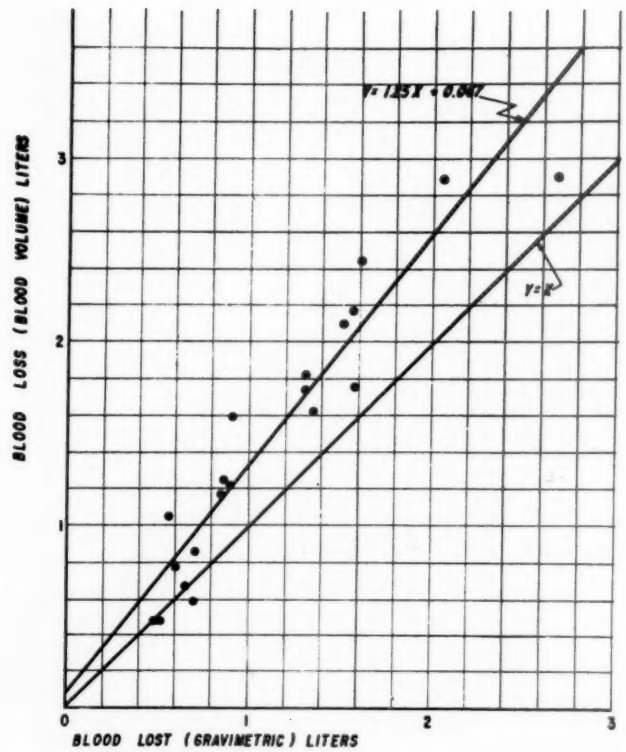

Fig. 2.—Diagram showing the correlation between the operative blood loss determined by the gravimetric method and the one estimated through the determination of the blood volume.

TABLE II

CASE NUMBER	HEMATOCRIT (PER CENT)		BLOOD VOLUME (LITERS)		DIFFERENCE	BLOOD TRANSFUSED (LITERS)	BLOOD LOST B.V.* (LITERS)	BLOOD LOST GRAV.† (LITERS)
	PREOP.	POSTOP.	PREOP.	POSTOP.				
1	26.7	24.5	3.39	2.66	0.73	0.44	1.17	0.84
2	35.6	28.5	3.72	2.56	1.16	1.28	2.44	1.60
3	38.1	36.8	2.66	2.43	0.23	0.35	0.58	0.70
4	36.1	33.5	3.71	2.71	1.00	0.75	1.75	1.57
5	41.0	41.6	4.33	3.92	0.41	0.71	1.11	0.90
6	43.2	45.2	4.16	4.12	0.04	0.44	0.48	0.50
7	44.5	47.0	3.88	3.27	0.61	0.44	1.05	0.56
8	42.5	43.0	3.40	3.37	0.03	0.45	0.48	0.52
9	48.5	43.5	5.40	4.75	0.65	2.25	2.90	2.67
10	43.0	44.5	5.20	4.40	0.80	0.79	1.59	0.90
11	44.0	46.7	4.15	3.98	0.07	0.71	0.78	0.60
12	44.0	42.0	3.55	3.35	0.20	0.66	0.86	0.70
13	41.0	45.0	3.90	3.40	0.50	1.23	1.73	1.30
14	35.5	37.7	3.78	2.65	1.13	1.76	2.89	2.05
15	40.5	41.0	4.37	3.37	1.00	1.10	2.10	1.50
16	37.0	41.5	3.75	3.60	0.15	1.10	1.25	0.85
17	41.6	42.3	3.33	3.33	0.00	0.66	0.66	0.65
18	42.8	39.0	4.10	3.35	0.75	1.07	1.82	1.30
19	42.5	38.5	3.91	3.13	0.78	1.39	2.17	1.55
20	42.5	40.0	3.80	3.38	0.42	1.22	1.62	1.34

*As determined by the difference between preoperative and postoperative blood volume plus blood transfused.

†As determined by the method described in the text.

TABLE III. STATISTICAL DATA

1.	Number of patients	$N = 20$
2.	Correlation coefficient (linear)	$r = 0.95$
	z transformation	$z = 1.84$
	Standard error of z	$s_z = 0.024$
		$z/s_z = 7.6$
3.	Regression equation	$Y = 1.25\ X + 0.067$
	Standard error of Y (estimated from X)	$Sy.x = 0.238$ liter
4.	Interceipt	$b = 0.067$ liter
	Standard deviation of interceipt	$s_b = 0.13$
	t value for b being different from 0	$t_b = 0.51$
	p value for t_b	greater than 0.5
5.	Slope	$m = 1.25$
	Standard deviation of slope	$s_m = 0.103$
	t value for m being different from 1	$t_m = 2.43$
	p value for t_m	$= 0.024$

the blood loss according to the determination of the blood volume. The correlation coefficient is high ($r = 0.95$). The statistical significance was analyzed by studying the "*z* distribution." This makes it possible to generalize the correlation of the cases studied to an infinite number of cases. When *z* is 3 or more times higher than its standard deviation, the correlation has statistical significance. In our case *z* is 7.6 times its standard deviation. This permits us to say that there is a statistically significant high correlation between both methods (the gravimetric method and using the blood volume) employed to determine the operative blood loss; and that if we study a larger number of cases this correlation is going to remain statistically significant.

We have studied the equation of the regression line in order to be able to know the blood loss that could be found by determining the blood volume (Y) knowing the blood loss determined by the gravimetric method (X). The regression equation is as follows: $Y = 1.25\ X + 0.067$ (X and Y expressed in liters). The regression line does not pass through the origin of the system of coordinates, but rather through $Y = 0.067$ liters. This value has no statistical significance. It is simply random, so we can simplify the foregoing formula as follows: $Y = 1.25\ X$. As can be seen in Fig. 2, there is a correlation between the blood loss determined by the gravimetric method and the one determined with the blood volume, and this correlation is maintained regardless of the quantity of blood lost. This enables us to affirm that the gravimetric method is adequate as a means of determining the operative blood loss.

From our data we can arrive at the conclusion that the blood loss estimated by the difference in blood volumes is 1.25 higher than the blood loss estimated by the gravimetric method, and if we consider the former as the index of the true operative blood loss, it would be necessary to restore the blood loss determined gravimetrically, plus 25 per cent, by means of a transfusion.

SUMMARY AND CONCLUSIONS

There is no correlation between the difference in the pre- and postoperative hematocrit and the blood loss occurring during the surgical operation which is not restored.

There is a high correlation between the operative blood loss determined by the gravimetric method and the one estimated through the determination of the blood volume. This correlation is linear, has a high statistical significance, and remains uniform within all the values studied. This work confirms the validity of the gravimetric method as an adequate and simple way of determining the operative blood loss.

The regression equation that has been calculated demonstrates that the value of the blood loss determined gravimetrically, plus 25 per cent, is equivalent to the true operative blood loss.

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AN AID IN THE APPLICATION OF PRESSURE DRESSINGS

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THE application of massive pressure dressings requires several assistants to support the patient. If he is improperly held, inadequate dressings may result, with dangerous as well as uncomfortable wadding and constrictions.

A light frame has been devised to overcome these difficulties. It is of simple design and inexpensive. It can readily be set up or dismantled.

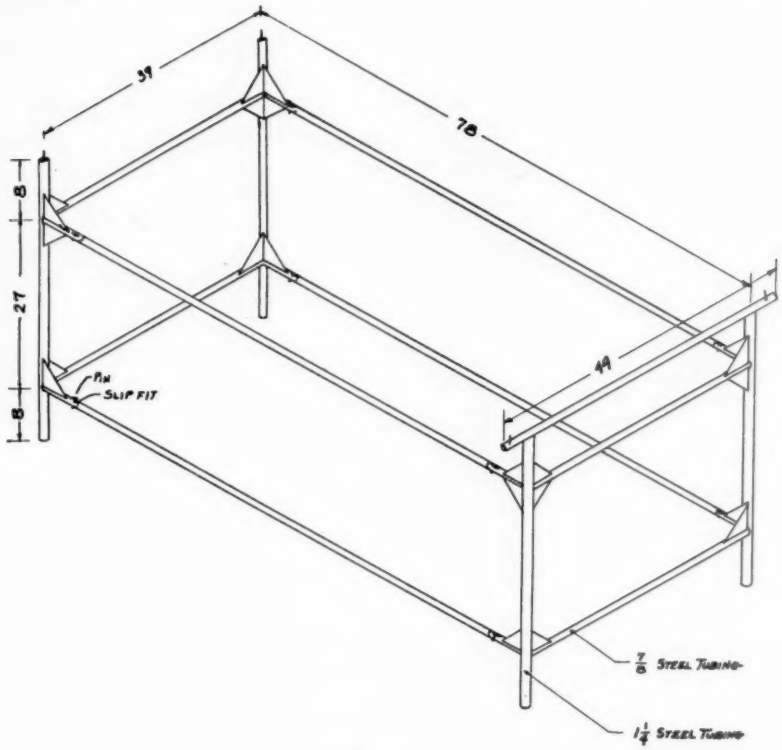

Fig. 1.

In principle the patient is suspended on two thin strips of flexible steel which form a St. Andrew's cross. These slats are supported at their ends by a light metal framework that surrounds a standard operating table. They are well powdered with Bio-Sorb and support the patient during the dressing, following which they are removed.

The patient's old dressings are removed on the stretcher bringing him to the room and the wounds or injuries are cared for as desired. The patient

Received for publication Oct. 10, 1958.

in then lifted onto a clean dressing in the proper position on the crisscross metal slats which are resting on the operating table.

The operating table is then lowered, the patient being supported with his dressing on the slats. The dressing is turned up over the patient and wrapped in place. The table is then elevated and the slats withdrawn. The details can be readily visualized from the accompanying illustrations.

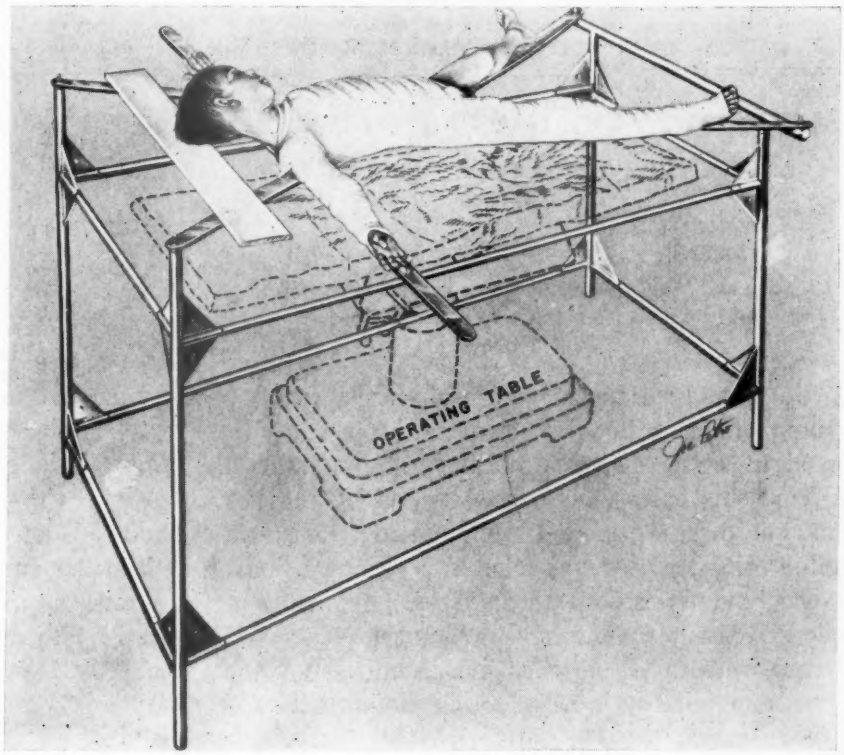

Fig. 2.

In conclusion, a metal frame to aid in applying large dressings is described. It is simply constructed, readily dismantled, and fits a standard operating table. It has been of immeasurable help over the past three years.

Pediatric Surgery

CONDUCTED BY MARK M. RAVITCH, M.D.

RECTAL BIOPSY IN THE DIAGNOSIS OF HIRSCHSPRUNG'S DISEASE

EXPERIENCE WITH ONE HUNDRED BIOPSIES

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THE diagnosis of Hirschsprung's disease may be impossible to establish by routine techniques in some children and in many infants. While the history, physical signs, and roentgen findings establish the diagnosis in the majority of children, some cases fail to be detected by these methods. In the majority of infants the disease remains undiagnosed by routine methods. Since absence of ganglion cells in the distal colon is a constant finding in Hirschsprung's disease, it occurred to us 5 years ago to remove a bit of rectal wall as a biopsy.[2] The status of the ganglion cells in this material would establish the diagnosis. Considerable clinical experience has accumulated with this procedure, and it can be recommended as a safe, reliable diagnostic aid.

INDICATIONS

Rectal biopsy is indicated in cases of chronic constipation where the possibility of Hirschsprung's disease cannot be eliminated by barium enema. Habit constipation may become so severe that abdominal distention and considerable colonic enlargement occur. Before dismissing these children from consideration as candidates for correction by surgery and undertaking a long course of habit clinic treatments, one may use the rectal biopsy as a simple definitive test to rule out a myenteric ganglion defect in the distal colon.

Another group of children in whom this test is indicated comprises the unusual cases of Hirschsprung's disease. Patients with short, low lesions involving only the distal 2 or 3 inches of rectum may have persistent constipation while the radiographic findings are equivocal. Some children with low lesions

Received for publication Dec. 2, 1958.

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are so well cared for by their parents with daily rectal irrigations that colonic dilatation is minimal and a roentgenographic diagnosis of congenital megacolon is impossible.

Hirschsprung's disease is most difficult to manage successfully in infants under one year of age. It is in this group of patients that the rectal biopsy has been found most valuable. The newborn infant with Hirschsprung's disease often does not have the characteristic narrow distal colon or widely dilated proximal colon which is pathognomonic of this disease. The entire colon and even part of the ileum may lack ganglia in the myenteric plexus; and in such instances, a diagnosis cannot be made by barium enema. An occasional case of meconium peritonitis resulting from spontaneous perforation of the colon has Hirschsprung's disease as the underlying pathology. There is a small group of infants with Hirschsprung's disease that present with symptoms of chronic diarrhea and failure to do well during the first year. The liquid stool may be mixed with blood from superficial ulcerations of the mucosa. Without the usual symptoms of constipation and recurrent intestinal obstruction, the diagnosis is difficult to make. In all these unusual situations rectal biopsy provides the only means of making an accurate diagnosis of Hirschsprung's disease. Accuracy in diagnosis is essential for it is now possible to cure patients with this disease by resection of the aganglionic segment of colon.

Occasionally a laparotomy is performed on an infant for symptoms of intestinal obstruction and a colostomy is made without a definitive diagnosis being established. The diagnosis of congenital megacolon by barium enema is difficult after colostomy since dilatation of the colon disappears. Such patients present an urgent clinical problem. If they do not have Hirschsprung's disease, the colostomy can be closed with the assurance that they will do perfectly well. On the other hand, if they have Hirschsprung's disease, closure of the colostomy would be ill advised and lead to further problems for the child. In such situations a rectal biopsy is imperative to determine proper treatment.

METHOD OF PERFORMING BIOPSY

The technique of rectal biopsy is important if one is to obtain a satisfactory specimen. The external approach to the anal sphincter through the skin and fat of the buttock has been advocated.[3] With this approach it is more difficult to obtain an adequate specimen, and complications such as fistula-in-ano may follow. Inadvertent damage to the sphincter innervation may occur. At the beginning of our experience with biopsy, tissue was taken from the internal anal sphincter approached from the lumen of the anal canal. The pathologist found this tissue difficult to interpret since there is no consistent relationship between the muscle bundles and the myenteric plexus at this level. If ganglion cells were not found, multiple histologic sections were necessary to make sure they had not been overlooked. Improvements were sought by studying specimens from 10 cadavers. Just above the internal anal sphincter, every section of the rectal wall contained ganglion cells. The relationship of the ganglion cells in the myenteric plexus between the inner circular and outer longitudinal muscular coats made it possible for the pathologist to determine

Fig. 1.

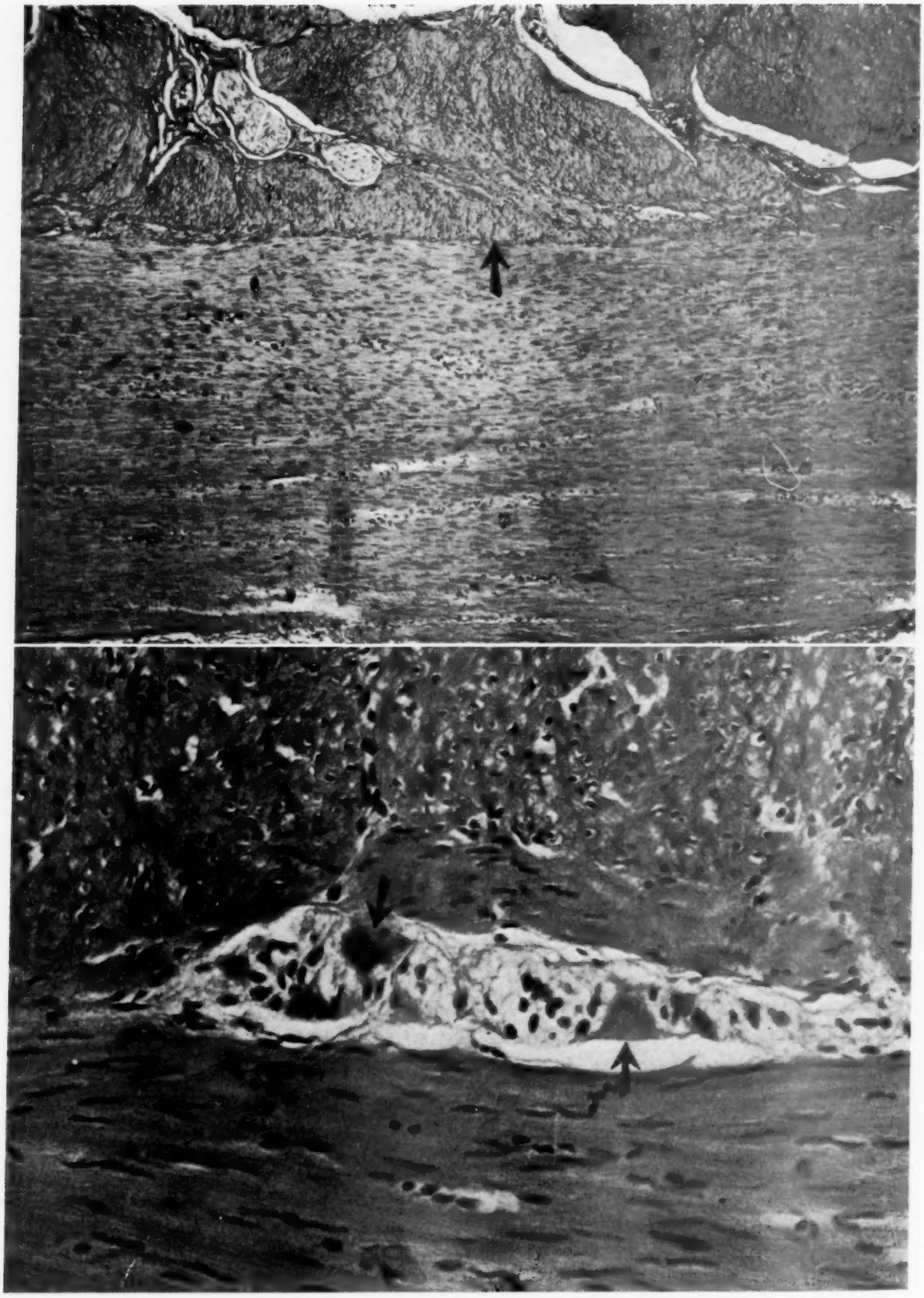

Fig. 2.

Fig. 1.—Photomicrograph of histologic section of the rectal wall obtained from a control specimen. The longitudinal muscles are sectioned transversely in the middle of the figure. In the lowest part of the figure, the circular muscles are sectioned in the direction of their fibers. Between the two layers of muscle, the myenteric plexus is seen.

Fig. 2.—Higher magnification of the myenteric plexus with two ganglion cells clearly seen. (From Swenson, O.: Pediatric Surgery, New York, 1958, Appleton-Century-Crofts, Inc.)

from examination of routine histologic section whether ganglion cells were present or absent (Figs. 1, 2, and 3). Care in securing a proper biopsy specimen permitted the pathologist to render an immediate report, using a rapid, or frozen section, technique. Consequently, our technique was revised so that a specimen was obtained 2 cm. above the mucocutaneous line.

Patients to have a rectal biopsy are prepared with rectal irrigations to remove all material from the lower colon. No special diets, preoperative antibiotics, or laxatives are used. A general anesthesia is administered to prevent pain and allow the anal sphincter to be widely dilated. The patient is turned on the side and the hips are flexed (Fig. 4, *A*). The perineum and rectum are prepared with pHisoHex and aqueous Zephiran. A gauze sponge is placed in the upper rectum to prevent feces from contaminating the operative field.

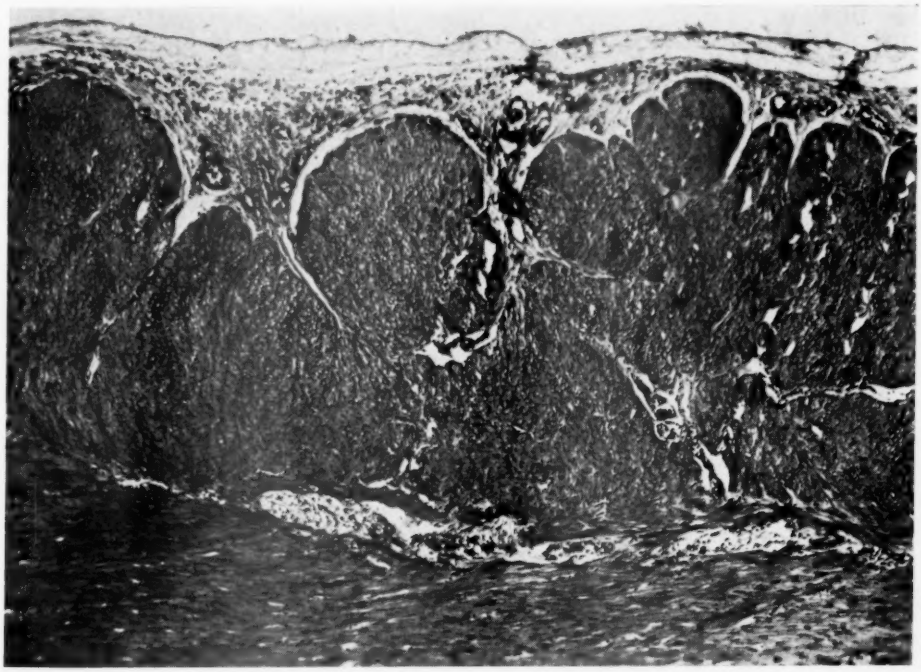

Fig. 3.—Photomicrograph of a histologic section of the rectal wall from a patient having Hirschsprung's disease. The myenteric plexus between the muscular coats contains no ganglion cells. (From Swenson, O.: Pediatric Surgery, New York, 1958, Appleton-Century-Crofts, Inc.)

A Sims retractor is helpful to expose the rectal wall. The site for the biopsy is chosen on the lateral wall, 2 or 3 cm. above the mucocutaneous margin. The anterior rectal wall is avoided to prevent injury to the vagina, prostate, or urethra. Traction on the buttock and perianal skin will bring the rectal wall into view. Traction sutures of fine silk are placed on each side of the biopsy site to aid in maintaining the rectal wall in the field (Fig. 4, *B*). The mucosa is incised for 2 cm. and by blunt dissection separated from the muscular layer. A triangular piece of muscular wall, 5 by 10 mm. is removed; care is taken that both the circular and longitudinal layers are included in the biopsy material

(Fig. 4, *D*). The specimen should be inspected to make certain that both muscular coats with the interlaminar layer of autonomic nerves and ganglia between them are included. There is no harm in removing some of the mucosa as well. This will give the pathologist an opportunity to study the Meissner's as well as Auerbach's plexus. Occasionally, a blood vessel large enough to grasp with a hemostatic forceps is encountered. Usually, temporary hemostasis is accomplished by pressure with a gauze sponge.

The defect in the rectal wall is closed with interrupted sutures (Fig. 4, *E*). A layer of 4-0 silk is used to close the muscular coats, and 4-0 chromic catgut is used for the mucosa (Fig. 4, *F*). Hemostasis is complete with this technique. No postoperative precautions as to diet or bowel management are observed. Antibiotics are not administered, and the patient is discharged from the hospital the day following the biopsy. One advantage of taking the biopsy several centimeters above the mucocutaneous line is that it is in the segment of bowel to be removed if the operation for Hirschsprung's disease is performed.

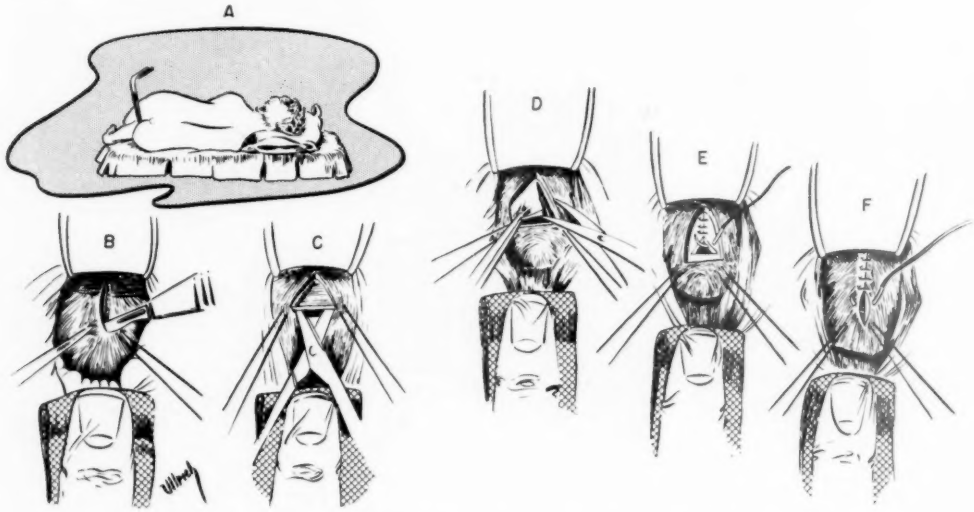

Fig. 4.—*A*, Drawing indicating position of patient for rectal biopsy. *B*, The lateral rectal wall is incised 2 cm. above mucocutaneous margin. *C*, Care is taken to include both circular and longitudinal fibers in biopsy. *D*, A triangular piece of muscle wall is removed for histologic study. *E*, The muscular incision is closed with silk sutures. *F*, The mucosa is approximated with chromic catgut sutures.

The pathologist, in evaluating the biopsy, faces a situation wherein a positive diagnosis, and consequently surgical intervention, is based on finding no ganglion cells. The normal myenteric plexus of Auerbach contains sufficient numbers of neurons to make their identification in the biopsy a matter of relative ease. The ganglia of the submucosal plexus of Meissner, on the contrary, are far less conspicuous even in the normal case. In the face of these practical considerations, therefore, the pathologist cannot be satisfied with less than an adequate biopsy inclusive of both muscle layers before he may report the absence of ganglionic elements which validates the diagnosis of Hirschsprung's disease. Inclusion of mucosa in the biopsy is to be encouraged for it gives the pathologist an opportunity to study Meissner's plexus as well as Auerbach's. It should

be emphasized that a certain degree of familiarity with the histology of this area is necessary and that reliable evaluation may on occasion require a thorough examination of several permanent microscopic sections.

We have evaluated the results from 100 consecutive cases in which rectal biopsy has been performed. Experience with the operation has extended over a period of 5 years. In 38 cases, the diagnosis of Hirschsprung's disease was made with the aid of the biopsy and was verified later in the resected specimen. Sixty-two patients had chronic constipation or some other condition to account for their symptoms. There was no mortality in the series. The morbidity was negligible; one patient early in the series was returned to the operating room for additional hemostatic sutures. This occurred before the present technique of suturing the defect was used. No perirectal infections or fistulas-in-ano were seen. There was no disturbance of anal continence. Resection for Hirschsprung's disease was occasionally performed the same day as the biopsy or was done several days later depending upon the condition of the patient. During the 5-year period covered by this study, 110 cases of Hirschsprung's disease were treated operatively. In 38 cases or about one-third of this group, rectal biopsy was performed to establish the diagnosis. Biopsy was probably used more frequently in this series than would be indicated ordinarily since many were problem cases referred by other physicians.

SUMMARY

A safe, reliable technique for rectal biopsy is described. Both muscular coats of the rectal wall, 2 to 3 cm. above the mucocutaneous junction must be included in the specimen. Biopsy provides the sole means of establishing the diagnosis of Hirschsprung's disease in most infants and in some children with atypical histories and nonspecific roentgen findings. In 100 consecutive biopsies in patients considered possibly to have Hirschsprung's disease a positive diagnosis was made in 38. All 38 were operated upon, and in all the operative specimen showed the typical lesion of Hirschsprung's disease.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

SIXTY PENETRATING WOUNDS OF THE HEART

CLINICAL AND EXPERIMENTAL OBSERVATIONS

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INTRODUCTION

LARREY, Napoleon's surgeon, in 1829 first successfully used pericardiocentesis in the treatment of acute pericardial tamponade resulting from a penetrating wound of the heart.[20] In 1896, Rehn[27] first successfully sutured a laceration of the heart.

In the past several decades, following the lead of Blalock and Ravitch,[7, 26] Elkin and Campbell[14] and Cooley and his co-workers[9] have advocated pericardial aspiration as the initial treatment of penetrating wounds of the heart; whereas Griswold and Drye,[16, 17] Maynard and associates[23, 24] have strongly favored immediate operative repair.

The experiences of a number of groups are summarized in Table I. Although a difference of opinion has existed regarding the preferability of operative or nonoperative management, these experiences have made clear that both forms of therapy can be effectively employed. The choice will be influenced by various factors, which are discussed.

Clinical observations in 60 cases of penetrating heart wounds from The Johns Hopkins Hospital in the past 22 years (1937-1959) are reported.

Pertinent experimental observations concerning the pathologic physiology of acute pericardial tamponade are applied to its treatment.

The incidence of constrictive pericarditis after nonoperative treatment of penetrating heart wounds is presented and its significance is considered.

CLINICAL OBSERVATIONS

Penetrating wounds of the heart may be complicated by (1) acute pericardial tamponade alone, (2) severe extrapericardial hemorrhage alone, or

Received for publication Jan. 26, 1959.

(3) a combination. Table II lists the 1937-1959 mortality rates at The Johns Hopkins Hospital according to mode of injury (gunshot or stab) and complication (as above). Sixty patients arrived alive and received treatment. More injuries were by stabbing. The mortality was higher in gunshot

TABLE I. MORTALITY RATES FROM VARIOUS CLINICS OVER THE PAST TWO DECADES

YEAR	SERIES	NUMBER OF CASES	DEATHS	PER CENT MORTALITY
1939	Bigger[5]	17	6	35.3
	Questionnaire*	141	70	49.6
1941	Elkin[12] (operative)	38	16	42.1
1944	Elkin[13] (operative)	23	5	21.7
1951	Elkin and Campbell[14] (non-operative)	17	1	5.9
	Elkin et al. totals	78	22	28.2
1952	Maynard et al.[23]	81	46	57.0
	Operative therapy	61	26	42.7
1954	Griswold and Drye[16]	108	41	37.9
	Operative therapy	82	20	24.4
1955	Cooley et al.[9]			
	Pericardial aspiration	28	3	10.7
	Operative therapy	14	7	50.0
	Supportive therapy	15	7	46.7
	Cooley et al. totals	57	17	29.8
1959	Johns Hopkins Hospital			
	Nonoperative therapy	40	4	10.0
	(Cardiac tamponade alone)	31	0	0.0
	Operative therapy	20	6	30.0
	Totals	60	10	16.7

*Bigger's questionnaire: Results from American Surgical Society, Southern Surgical Society, and American Association of Thoracic Surgery.

TABLE II. MORTALITY RATES BY MODE OF INJURY AND COMPLICATION IN 60 PENETRATING WOUNDS OF THE HEART (THE JOHNS HOPKINS HOSPITAL, 1939-1959)

MODE OF INJURY	COMPLICATION	CASES	DEATHS	MORTALITY (PER CENT)
Stab wounds (88.3%)	Acute tamponade	36	0	0.0
	Hemorrhage	5	2	40.0
	Both	12	4	33.3
	Total	53	6	11.3
Gunshot wounds (11.7%)	Acute tamponade	4	1	25.0
	Hemorrhage	-	-	-
	Both	3	3	100.0
	Total	7	4	57.2
All wounds	Acute tamponade	40 (66.7%)	1	2.5
	Hemorrhage	5 (8.3%)	2	40.0
	Both	15 (25.0%)	7	46.7
	Total	60	10	16.7

wounds. More patients had acute tamponade alone with stab wounds. The mortality rates were much higher with extrapericardial hemorrhages than with tamponade alone. Blood was present in the pericardium in 94 per cent

of all cases. Either a ventricle or great arterial vessel was penetrated in 9 of the 10 persons who died. The over-all mortality was 16.7 per cent. The mortality with acute tamponade alone (40 patients) was only 2.5 per cent.

There was not a single mortality in the group with acute tamponade alone treated by pericardial aspiration (31 cases). Approximately one-half of the 20 patients with severe extrapericardial hemorrhage were treated by nonoperative means and one-half by operative with just less than a 50 per cent mortality by each method. The over-all mortality was 45 per cent (9 deaths in 20 cases).

Another seventy-three persons with penetrating heart wounds were dead on arrival (54.9 per cent of the total). No form of therapy was attempted. Sixty per cent or twice as many of these had extrapericardial hemorrhage. A great arterial vessel or ventricle was penetrated in 96 per cent of the number. This means that, of the total of 83 persons dead on arrival or dying after arrival, 95 per cent had this type of injury.

Penetrating wounds of the heart can cause other cardiac injuries, such as laceration of coronary arteries with myocardial infarction, damage to intracardiac or great vessel valves, or division of the conduction system. These can cause immediate or early death, but in actuality occur infrequently. Of the 60 patients arriving alive, two had coronary arterial injuries with later death (one of these had a pulmonary valve leaflet lacerated also). A third who died had a ventricular septal laceration. Of the 73 arriving dead, only two had coronary arterial and aortic valve lacerations.

CONSTRICTIVE PERICARDITIS

The persistence of an elevated venous pressure, distant heart sounds, and cardiac enlargement in the patient who has been benefitted by pericardial tap raises the question of surgical evacuation of a clotted hemopericardium to obtain more adequate acute relief and to insure against the later development of constrictive pericarditis.

The development of constrictive pericarditis after hemopericardium is theoretically always possible. Its true incidence is not known. McKusick and associates[21] reported 3 cases of this later complication from The Johns Hopkins Hospital, one after a gunshot wound of the heart, one after a stab, and one after a blow to the chest. In their paper, 10 other cases were compiled from the literature. Cooley and co-workers[9] from 57 wounds cited 2 additional cases. Ada and associates[1] and Barker and Johnston[2] reported single cases, making a total of 17 cases, known to us.

In the present group of 60 penetrating wounds of the heart, two are known to have developed chronic constrictive pericarditis (one at 6 months after gunshot, the other 4 years after stab wound). It was possible to follow for a period from 5 to 20 years 20 of the 40 patients with tamponade treated nonoperatively in the present series. Of this number two developed

symptomatic constrictive pericarditis requiring decortication, an incidence of 10 per cent in the 20 followed or 5 per cent in the whole group. Two other patients developed pericardial effusion requiring pericardial aspiration several weeks after the initial injury. Each of these has been followed for over 4 years without evidence of constrictive pericarditis. Drs. Mark Ravitch and Robert Mason carried out various tests including electrocardiograms and exercise tolerance in 7 of the above 20 cases who were followed. All showed normal results.

Drye and associates[11] followed 20 cases of 65 treated operatively. After an interval of 3 to 20 years, 12 were working. None had ventricular aneurysms, constrictive pericarditis, or defects ascribed to their wounds.

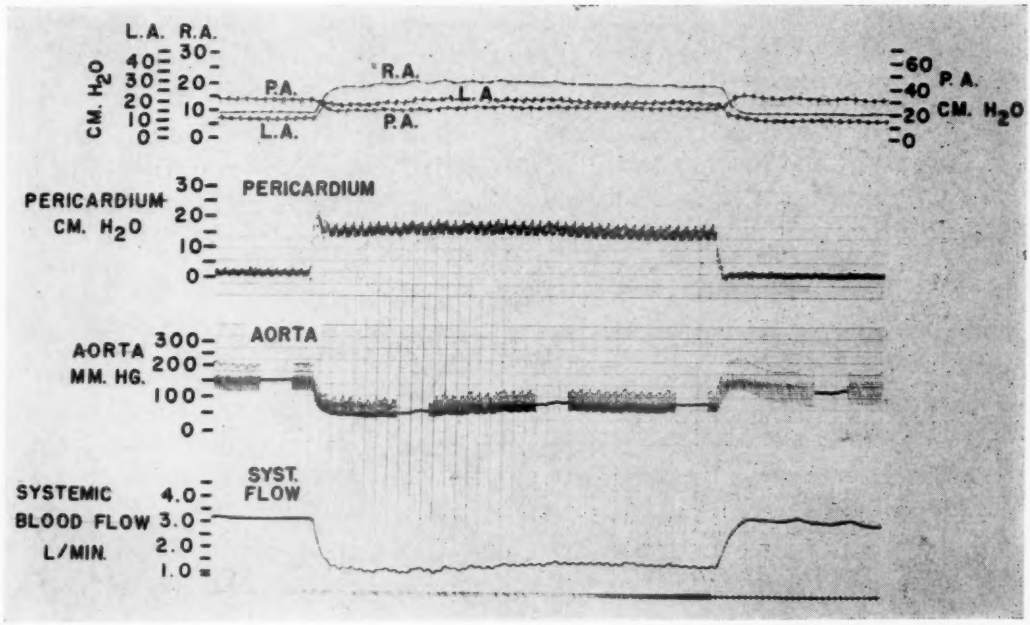


Fig. 1.—Dog weight 20.1 Kg. Heart weight 142 Gm. Tracing of hemodynamic effects of acute cardiac tamponade. P.A. = mean pulmonary artery pressure (scale at right). L.A. = mean left atrial pressure (scale at left). R.A. = mean right atrial pressure (scale at left). Aortic pressure is intermittently full pulse pressure and integrated mean pressure. Syst. Flow = cardiac output minus coronary flow. Time signal = 1 second. 130 c.c. air injected into the pericardium at beginning of signal and removed at end of signal.[18]

These data, while incomplete, indicate that the late complication of constrictive pericarditis following cardiac wounds merits consideration of surgical evacuation of the hemopericardium in the individual case, as described. However, the incidence is not so high as to contraindicate pericardial aspiration as a treatment for hemopericardium.

EXPERIMENTAL OBSERVATIONS

Hemodynamic Effects of Acute Pericardial Tamponade (Fig. 1).—Experiment 1 shows (a) the sudden rise in pericardial and atrial pressures and (b)

the sudden drop in aortic and pulmonary arterial pressures and systemic blood flow when acute pericardial tamponade was produced by 130 c.c. of air injected into the pericardial space of a 20 Kg. dog.

What is the mechanism producing these sudden hemodynamic changes? If, as stated by Cohnheim[8] and Beck,[4] the venoatrial segments of the heart collapse during acute pericardial tamponade with resulting obstruction to cardiac inflow at the venoatrial junctions; there should be a measurable pressure gradient across these junctions as tamponade is instituted.

Vena Caval–Right Atrial and Pulmonary Venous–Left Atrial Pressure Gradients With and Without Tamponade.—In a second type of experiment, there proved to be no measurable pressure drop across these junctions, even though a sensitive electronic manometric system was used, indicating that the hemodynamic defect in tamponade cannot be attributed to inflow obstruction at the entrance of the great veins through the pericardium.

Starling[29] stated that "hindrance to diastolic expansion" of the heart is the defect in tamponade. Additional experiments were done to establish that the crux of the pathology in acute pericardial tamponade resides within the mechanical pressure-volume characteristics of the pericardium and the influence of these characteristics upon right and left ventricles.

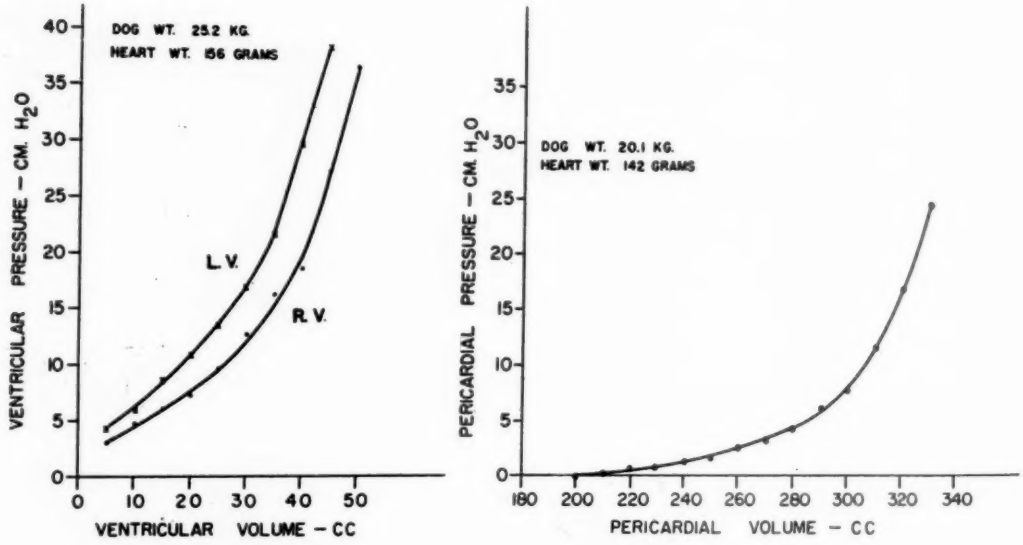


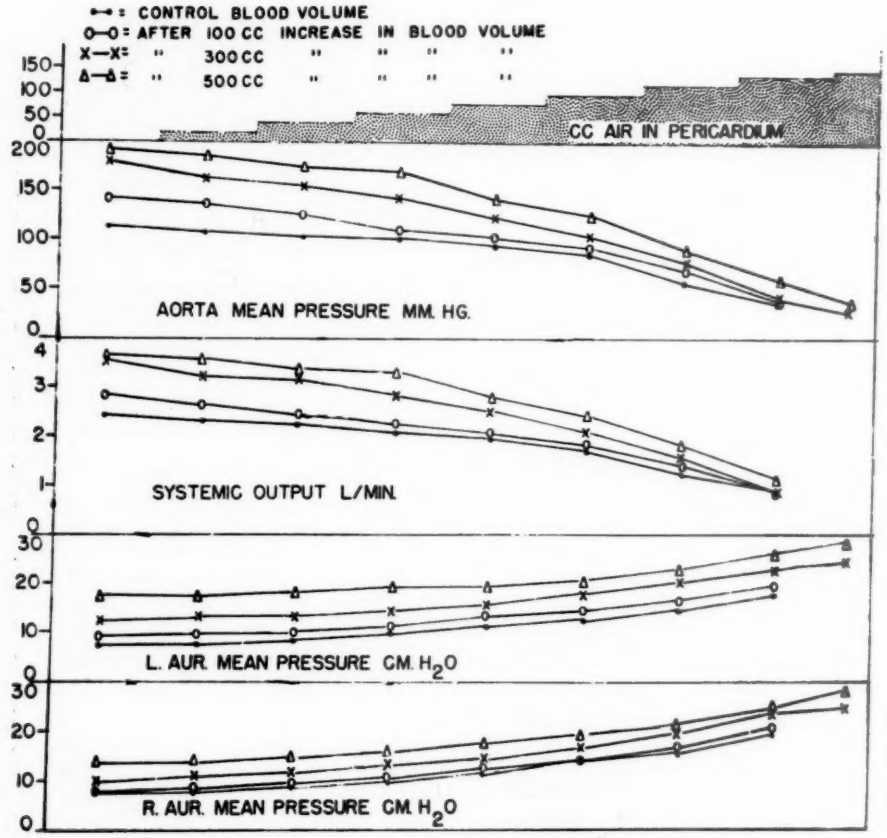
Fig. 2.—Volume-pressure relationships of dog pericardium and ventricles.[18]

Pericardial and Ventricular Pressure-Volume Curves and Their Significance in Acute Tamponade.—In a third type of experiment, pericardial pressure-volume curves were obtained in the dog (and in man) by stepwise filling of the pericardial space with saline (Fig. 2). Pericardial volumes and simultaneous pressures were recorded with each standard increment of saline. At first,

a sizeable fluid volume could be injected into the pericardial space with practically no pressure increase. Later, even the smallest increase in volume was associated with a very large pressure increase. The relationship of pericardial pressure to volume is seen to be exponential. Similar but steeper curves were obtained for the right and left ventricles.

In Fig. 2 note that 60 c.c. of fluid plus 150 c.c. (equivalent to gram weight of heart muscle) or 210 c.c. volume must reside within the pericardium before a measurable pericardial pressure effect begins to be observed. Considering this 60 c.c. as the blood volumes of the two ventricles with their atria at the end of ventricular diastole, this means that each ventricle can fill to about 25 c.c. at a rather low pressure. (Right ventricle with 25 c.c. has pressure of 8 cm. H_2O at atmospheric base line or about 0 to 1 cm. H_2O when in the closed chest.) This ventricular filling can take place without pressure being exerted against the pericardium. If 90 c.c. of fluid volume enters the pericardial space (150 c.c. heart weight plus 60 c.c. intracardiac volume plus 90 c.c. pericardial fluid equals 300 c.c. within the pericardium), there is a very steep rise in pericardial pressure for any further volume increase, whether intra- or extracardiac. Even an added 25 c.c. (see 325 c.c. on the pericardial curve) requires 20 cm. H_2O pressure. Observe that at the 320 c.c. volume mark on the pericardial pressure-volume curve, the pericardial pressure is 17 cm. H_2O. At this point both pericardial and intraventricular pressure will be the same and rise together, since both sites are subject to the pericardium's pressure-volume characteristics. Because the effective pressure for filling of the ventricles is pericardial pressure subtracted from intraventricular pressure, it is at this point where effective ventricular filling pressure approaches zero. If the pericardial space becomes filled with blood after a penetrating cardiac wound, the pericardial pressure rises, as an external pressure counteracting that of the internal or intraventricular venous filling pressure in diastole. As stated previously an exponentially steeper portion of the pericardial pressure-volume curve is reached as more of the pericardial space is filled, until at the extraventricular or pericardial pressure of about 17 cm. H_2O the intraventricular diastolic filling pressure is effectively neutralized. The ventricular chambers inside the pericardium, now being under the full influence of the pericardium's pressure-volume characteristics, can fill only very little at the cost of very high filling pressures. At this critical point the circulation ceases at the maximal static pressure which the over-all circulatory system is capable of reaching without its ventricular pumps. This static pressure is 17 cm. H_2O throughout on the average, given a normal blood volume. Given a greater or lesser blood volume, the value of pericardial pressure at which the circulation of blood ceases is somewhat higher or lower accordingly. Additional experiments were done to demonstrate this relation between blood volume and the pericardial pressure level which produces circulatory failure in the presence of acute pericardial tamponade.

The Influence of Increasing Blood Volume During Acute Pericardial Tamponade.—Fig. 3 illustrates the changes in hemodynamics during serially increased tamponade in the presence of a normal blood volume, a normal blood volume plus 100 c.c. of blood, plus 300 c.c., and plus 500 c.c. At any level of mild-to-moderate tamponade, an increase in blood volume definitely raises aortic pressure and cardiac output but does little at levels of severe tamponade. Venous and atrial pressures, however, rise with increased blood volume in all degrees of tamponade. Left atrial pressure rises in parallel with right atrial pressure. It is of some interest that this is the single incidence in cardiac pathology when the right atrial pressure is a true indicator of pulmonary edemogenic levels in the left atrium.


CONTROL BLOOD VOLUME
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AORTA MEAN PRESSURE MM. HG.
SYSTEMIC OUTPUT L/MIN.
L. AUR. MEAN PRESSURE CM. H2O
R. AUR. MEAN PRESSURE CM. H2O

Fig. 3.—Effect of increasing blood volume with varying degrees of tamponade. Note that in mild tamponade (at the left in figure), increasing the blood volume elevates arterial pressures and cardiac output significantly and in severe tamponade (at the right in figure) there is no significant improvement with increased blood volume.[18]

The contractility of the heart muscle and the vasomuscular tone do not remain rigidly unaltered in the face of the changing metabolic state accompanying acute circulatory failure. At least one of the mechanisms called into play under such stressful conditions is the release of sympathetic neuromediators which can equate the effect, on the heart, of a blood volume

increase in terms of a constrictive vascular volume decrease. In addition, myocardial contractility can be augmented by sympathomimetic amines.[28]

A fourth type of experiment has been conducted to demonstrate that the contractility of the heart and the peripheral vascular smooth muscle tone can be altered by sympathomimetic amines during tamponade, thereby producing some hemodynamic benefit.

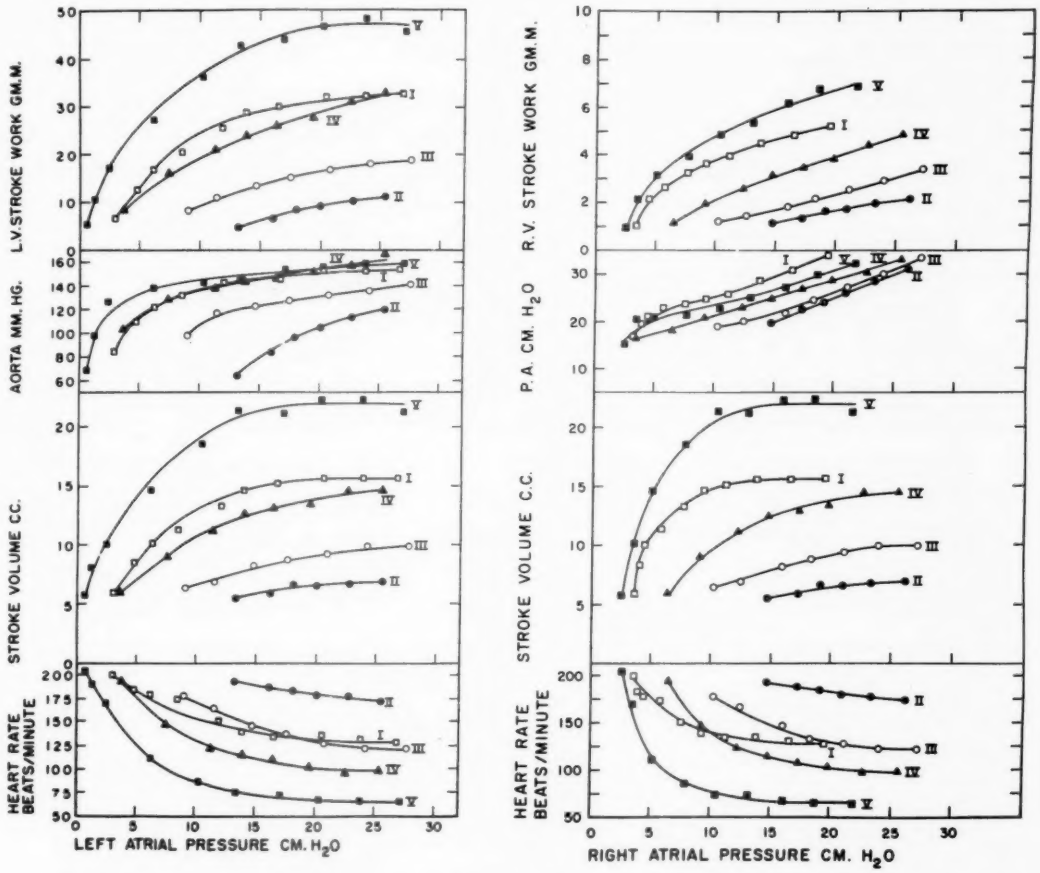

Fig. 4.—15.8 Kg. dog. Curves obtained as blood was transfused into a femoral vein from a reservoir, the height of which was stepwise raised during time of each curve. Reservoir was lowered and dog bled to control level between each curve. □—I—Control curve; ●—II—after tamponade; ○—III—after Aramine 0.05 mg./Kg. body weight i.v. while same degree of tamponade was maintained; ▲—IV—after a second injection of Aramine, 0.10 mg./Kg. with the same degree of tamponade; ■—V—postcontrol curve after the release of tamponade, Aramine still in effect. (From Binion, J. T., Morgan, W. J., Jr., Welch, G. H., and Sarnoff, S. J.: Effect of Sympathomimetic Drugs in Acute Experimental Cardiac Tamponade, Circulation Research 4: 706, 1954.)

The Hemodynamic Influence of Cardiovascular Stimulants (Sympathomimetic Amines) During Acute Pericardial Tamponade.—Data obtained by Binion, Sarnoff, and their associates[6] by the same techniques of study in the presence of tamponade reveal that sympathomimetic amines (like Aramine and Wyamine*) raise aortic pressure and cardiac output (also stroke volume) as ventricular end diastolic (atrial mean) pressures are reduced (Fig. 4). Cooley and co-workers[9] had similar results with norepinephrine.

*Merck Sharp & Dohme, Inc., and Wyeth Laboratories, Inc., Philadelphia.

DISCUSSION OF TREATMENT

The treatment of penetrating wounds of the heart consists of pericardial aspiration and supportive therapy or of surgical repair or of both. The factors to be considered in making the choice of management are of two types. The first is simply the availability of surgical personnel and facilities. The second and basically important is the existent complication; namely, acute pericardial tamponade or severe extrapericardial hemorrhage or both.

The diagnosis of severe extrapericardial hemorrhage from a wound of the heart may be made in the patient with a penetrating injury who has a low or normal venous pressure and arterial hypotension in the presence of audible heart sounds and fluoroscopically visible heart pulsations. Needle aspiration of the pericardium is helpful as a diagnostic maneuver to assist in ruling out acute tamponade. Hemothorax may be detected by physical signs (and when feasible by x-rays). Prompt and adequate blood volume replacement by 5 per cent glucose, dextran, plasma, or blood, as available, is mandatory. Cardiovascular stimulants help temporarily. In many cases immediate thoracotomy and cardiorrhaphy are absolutely necessary. In all cases, an operating room and team should be alerted at the outset.

The diagnosis of tamponade will be suspect where venous pressure rises toward a range of 15 to 20 cm. H_2O or above. Distended veins will make the diagnosis in many cases without benefit of direct measurement. Heart sounds will be distant or absent, as will pulsations on fluoroscopy. It is helpful to place the patient at the beginning upon the fluoroscopy table for therapy as well as examination.

The most efficacious treatment of acute cardiac tamponade is implied from the experimental studies and includes several aspects: (1) pericardial aspiration, (2) intravenous blood volume expanders, and (3) intravenous or intracardiac stimulants. In some cases (4) thoracotomy for evacuation of the pericardium and suture of the cardiac wound may be necessary.

The experimental studies leave small doubt concerning the critical value of reduction of the hemopericardium in tamponade. They make understandable the often-seen dramatic clinical benefit of aspiration of as little as 5 to 25 c.c. of pericardial fluid.

The value of the intravenous administration of blood volume expanders in the treatment of hemorrhage in general has been unequivocally accepted, but in the treatment of acute cardiac tamponade with some debate.[5, 9, 10, 12, 13, 17, 30]

It was for this reason that its spectrum of application was examined experimentally. In the presence of anything less than the most severe tamponade, it would appear to be of appreciable help, the degree of help being the greater, the smaller the degree of tamponade. The expansion of blood volume is not the critical factor in the therapy of acute tamponade, since with extremely severe tamponade it is devoid of efficacy. Whether it will be of

benefit cannot be adjudged by the patient's initial arterial or venous pressures alone or together. It should be instituted at the outset in all cases and its effect noted. Expanding the blood volume will further elevate venous pressure. If the venous pressure should rise markedly without a good response in arterial pressure, it may prove less wise to continue. The peripheral venous pressure in acute cardiac tamponade is a close approximation of pulmonary venous pressure as shown by Metcalfe, Burwell, and their associates[25] and serves as a warning against levels which produce pulmonary edema.

Cardiovascular stimulants in the treatment of hemorrhage have a definite role, especially as a holding maneuver until blood volume replacement can be effected.[28] As an adjunct in the treatment of acute cardiac tamponade, their place until recently had not been entirely established.[5, 12, 19] The experimental data cited[6, 9] corroborates the clinical impression of their usefulness.

OPERATIVE VERSUS NONOPERATIVE TREATMENT

The case against nonoperative treatment of cardiac wounds has been stated along these lines[16]: (a) blind pericardial aspiration is dangerous, (b) secondary hemorrhage or cardiac aneurysms may develop,[22] (c) chronic constrictive pericarditis may result from residual hemopericardium, (d) clot prevents effective aspiration of the pericardium, (e) other injuries are often associated with the cardiac wound, demanding surgical exploration of the abdomen and so forth anyway.

In several large series[7, 9, 14, 26] including the present one in which nonoperative therapy has been applied, these objections have not been found to be formidable. Of our 40 patients treated by pericardial aspiration, only one had a coronary vessel injury (and at post mortem this was undoubtedly due to the original wound and not to the pericardial needle), none had a secondary hemorrhage or cardiac aneurysm, and two developed constrictive pericarditis from residual hemopericardium. One additional patient had a clot preventing effective pericardial aspiration. Of the 60 cases in this series only 4 were associated with other injuries (liver, stomach, and so forth) requiring surgical exploration. (This situation unequivocally offers an indication for operative management.)

The simplicity, low mortality, and low morbidity of the nonoperative treatment for a large segment of these patients, particularly those with tamponade, offers a practical rebuttal to the contention that all such wounds should have immediate surgical repair. On the other hand, the high rate of operability and better recent results[16, 23, 24] substantiate the virtue of operative treatment, particularly with severe extrapericardial hemorrhage. Apparently a higher percentage of patients have had this type of complication in those series in which operative treatment has been predominantly employed.

Felsenreich[15] pointed out that wounds involving ventricular laceration should be operated upon while those involving auricles should be treated

without surgery. That this is still a dictum to be reckoned with may be appreciated by the observations that 96 per cent of the cases arriving dead in our Accident Room and 90 per cent of the 10 arriving alive and later dying had ventricular or arterial great vessel injuries.

SUMMARY

Of 133 cases of penetrating wounds of the heart brought to The Johns Hopkins Hospital from 1937 to 1959, 60 arrived alive and were treated, with a mortality of 16.7 per cent. Clinical and postmortem observations in these cases are presented with experimental observations concerning the pathologic physiology of acute pericardial tamponade as applied to its treatment.

The major complications of penetrating wounds of the heart were acute pericardial tamponade alone (two-thirds of the cases), severe extrapericardial hemorrhage alone, or a combination of both. Blood was present in the pericardium in 94 per cent of all cases.

Mortality from gunshot wounds was greater than from stab wounds. It was much greater from severe extrapericardial hemorrhage than from pericardial tamponade alone. A great arterial vessel or ventricle was perforated in almost all cases where death occurred.

The critical value of aspiration of blood from the pericardium in acute pericardial tamponade is emphasized by the clinical and experimental data.

The physiologic rationale for the benefits of blood or blood volume expanders and sympathomimetic cardiovascular stimulants in acute pericardial tamponade is clarified by experimental observations.

The choice of treatment of penetrating wounds of the heart is dependent upon the existent complications:

1. Pericardial aspiration and supportive treatment appears preferable for acute pericardial tamponade alone. Cardiorrhaphy was necessary in only one-fourth of these cases. There was only one death in 40 cases, a 2.5 per cent mortality.

2. Operative treatment should be quickly resorted to for the more serious complication of severe extrapericardial hemorrhage, in those instances when the initial nonoperative treatment proves inadequate for definitive therapy. Cardiorrhaphy was necessary in one-half of these cases. The difference in statistics regarding results of operative versus nonoperative treatment of penetrating wounds can be accounted for in part by the difference in numbers of patients with severe extrapericardial hemorrhages in the various series.

The development of chronic constrictive pericarditis following acute tamponade treated by pericardial aspiration was observed in two instances. This incidence is not felt to be great enough to contraindicate the use of nonoperative therapy.

Figs. 1, 2, and 3 are reproduced from Isaacs, J. P., Berglund, E., and Sarnoff, S. J.: Am. Heart J. **48**: 66, 1954. Appreciation is expressed to Drs. Stanley J. Sarnoff and Erik Berglund for their collaboration with the experimental observations of acute tamponade.

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